PROTOCOL TITLE:

Nintedanib Plus Standard of Care Immunosuppression Versus Standard of Care Immunosuppression Alone in Patients with Progressive Fibrotic Myositis Associated - Interstitial Lung Disease: A Randomized, Double-Blind, Exploratory Trial

Short title: Myositis Interstitial Lung Disease Nintedanib Trial (MINT)

Clinical Phase: Exploratory (Pilot) Trial

Coordinating Center: University of Pittsburgh

Funding/Sponsor: Boehringer Ingelheim

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PRINCIPAL INVESTIGATOR:

Rohit Aggarwal, MD, MS (University of Pittsburgh)
3601 Fifth Avenue, Suite 2B
Pittsburgh, PA 15213
Phone: (412) 647-8708
aggarwalr@upmc.edu

CO-INVESTIGATORS

Chester V. Oddis, MD (University of Pittsburgh)
200 Lothrop Street
Pittsburgh, PA 15261
Phone: (412) 383-8861
cvo5@pitt.edu

Siamak Moghadam-Kia, MD, MPH (University of Pittsburgh)
200 Lothrop Street
Pittsburgh, PA 15261
Phone: (412) 648-9782
moghadamkias@upmc.edu

Dana P. Ascherman, MD (University of Pittsburgh)
200 Lothrop Street
Pittsburgh, PA 15261
Phone: (412) 383-8734
Dascher@pitt.edu

Vladimir Liarski, MD (University of Pittsburgh)
200 Lothrop Street
Pittsburgh, PA 15261
Phone: (412) 383-8000
Vliarski@pitt.edu

Daniel Sullivan, MD
3469 Fifth Avenue
Pittsburgh, PA 15213
Phone: (412) 692-2210
sullivandi@upmc.edu

Daniel Kass, MD
200 Lothrop Street
Pittsburgh, PA 15261
Phone: (412) 624-7225
kassd2@upmc.edu

Kevin Gibson, MD
3469 Fifth Avenue
Pittsburgh, PA 15213
Phone: (412) 624-7225
gibsonkf@upmc.edu

Tanya Chandra, MD
3601 Fifth Avenue, Suite 2B
Pittsburgh, PA 15213
Phone: (412) 383-8000
Chandrat3@upmc.edu

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
4.2 Study Schema	Revised total patient number from 134 to 70, along with each treatment group, 35 in each. Reduced the number of study sites from 15 to 11.	The funder, Boehringer Ingelheim, made this business decision to decrease total patients enrolled and not proceed with sites that not completed study initiation visits.
5.3.2, Exclusion Criteria 3a	Revised wording regarding time needing to stay on contraception following last dose of study drug. Updated from 28 days to 3 months.	Revision of timeframe made in consent and other section of the protocol, however this section was overlooked when update was previously made.
12.7, Sample Size	Revised total patient number from 134 to 70.	The funder, Boehringer Ingelheim, made this business decision to decrease total patients enrolled

TABLE OF CONTENTS

ABBREVIATIONS

1.0 INTRODUCTION

1.1 Disease Background

1.2 Nintedanib Background

1.3 Study Rationale

2.0 OBJECTIVES

2.1 Primary

2.2 Secondary

2.3 Hypotheses

3.0 STUDY ENDPOINTS

3.1 Primary Endpoints

3.2 Key Secondary Endpoints

3.3 Other Secondary Endpoints

3.4 Exploratory Endpoints

4.0 STUDY DESIGN

4.1 Description of the Study

4.2 Study Schema

4.3 Flow Diagram of the Clinical Trial Process

4.4 Study Design Diagram

4.5 Biobank

4.6 Other considerations

5.0 SUBJECT SELECTION

5.1 Eligibility Screening

5.2 Study Consent

5.3 Inclusion and Exclusion Criteria

5.3.1 Inclusion

5.3.2 Exclusion

5.4 Immunization during Nintedanib therapy

6.0 STUDY INTERVENTION / INVESTIGATIONAL AGENT

6.1 Nintedanib Description

6.2 Treatment Plan Dosing/Regimen

6.3 Dosage and Administration

6.4 Definition of Worsening Criteria

6.4.1 Myositis

6.4.2 ILD

6.4.3 Non-responder

6.5 Dose Modification and Toxicity Management

6.6 Storage

6.7 Study Drug Labeling

6.8 Blinding and Unblinding procedures

7.0 STUDY MEDICATION RISKS AND ADVERSE REACTIONS

7.1 Risks

7.2 Adverse Reactions

7.3 Other Potential Sides Effects of Research Procedures

8.0 ENROLLMENT AND STUDY VISITS – LOCAL SITE PATIENTS

8.1 Prescreening

8.2 Consent Process

8.3 Service Coordination / Equipment Courier

8.4 Visit 0 – Screening

8.5 Randomization
8.6 Visit 1 - Baseline
8.7 Visits 2, 3, 5, 6 (Weeks 4, 8, 16, 20)
8.8 Visits 4, 7 (Weeks 12, 24)
8.9 Visit 8 (Post-trial Phone Call)
8.10 Weekly Patient Tasks
8.11 Early Termination / End of Treatment
8.12 Unscheduled Visit
8.13 52-week phone call
8.14 Compensation

9.0 ENROLLMENT AND STUDY VISITS – REMOTE PATIENTS
9.1 Prescreening
9.2 Consent Process
9.3 Remaining visits

10.0 SUBJECT DISCONTINUATION
10.1 Stopping Rules for Nintedanib
10.2 Process for Subject Discontinuation

11.0 ADVERSE EVENTS MONITORING AND REPORTING
11.1 Adverse Event Definition
11.2 Serious Adverse Definition
11.3 Adverse Events of Special Interest
11.3.1 Definition of Hepatic Injury
11.4 AE/SAE/AESI Monitoring and Reporting
11.5 Intensity of Adverse Event
11.6 Causal Relationship of Adverse Event

11.7 Responsibilities of Adverse Event Reporting Boehringer Ingelheim

11.8 Pregnancy

11.9 Overdose

11.10 Other Safety Concerns

12.0 STATISTICAL CONSIDERATIONS

12.1 Statistical Design

12.2 Primary Aim and Endpoint

12.3 Stratification and Randomization

12.4 Patient Cohorts Used for Analysis

12.5 Full analysis set cohorts (FAS)

12.6 Statistical Analysis Plan

12.7 Sample Size Calculation and Justification

13.0 RETENTION OF RECORDS

REFERENCES/BIBLIOGRAPHY

APPENDICES

Appendix A: Clinical Worsening/Flare up

Appendix B: Schedule of Assessments – Local Patients

ABBREVIATIONS

Abbreviation	Term
ACR/EULAR	The American College of Rheumatology / European League Against Rheumatism
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society / European Respiratory Society
BI	Boehringer Ingelheim
BP	Blood pressure
CK	Creatine kinase
CMRN	Certified mobile research nurse
CRF	Case report form
CTD-ILD	Connective tissue disease-associated interstitial lung disease
CTD-ILD OMERACT	Outcome Measures in Rheumatology
DILI	Drug-induced liver injury
DLCO	Diffusing capacity of lung for carbon monoxide
DMSB	Data and Safety Monitoring Board
EMR	Electronic medical record
EOT	End of treatment
ET	Early termination
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
GC	Glucocorticoid
GGT	Gamma-glutamyl transferase
HR	Heart rate
HRCT	High-Resolution Computed Tomography
IIM	Idiopathic inflammatory myopathy
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis

Abbreviation	Term
IS	Immunosuppressant
LFT	Liver function tests
L-PF	Living with Pulmonary Fibrosis questionnaire
MA- ILD	Myositis-associated interstitial lung disease
PCWP	Pulmonary capillary wedge pressure
PF	Pulmonary fibrosis
PFT	Pulmonary function test
PH	Pulmonary hypertension
PM	Polymyositis
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient reported outcomes
PROMS	Patient reported outcome measures
PROMIS	Patient-Reported Outcomes Measurement Information System
REP	Residual effect period
RVSP	Right ventricle systolic pressure
RV	Right ventricle
SAE	Serious adverse event
SGRQ	St. George's Respiratory Questionnaire
SOC	Standard of care
SS	Study staff
SSc-ILD	Systemic sclerosis-associated interstitial lung disease
SpO2	Oxygen saturation
TR	Tricuspid regurgitation
ULN	Upper limit of normal

1.0 INTRODUCTION

1.1 Disease Background

Idiopathic Inflammatory Myopathy (IIM) (or myositis) is a heterogeneous group of systemic autoimmune disorders which primarily target muscle, skin, and lungs. Many patients with IIM [primarily polymyositis (PM), dermatomyositis (DM), and anti-synthetase syndrome (ASSD)] develop interstitial lung disease (ILD), a strong driver of quality-of-life impairment, morbidity, and mortality in these patients. The prevalence of ILD in myositis (myositis-associated ILD or MA-ILD) varies, but in certain subgroups of IIM, ILD reportedly occurs in up to 90% of patients. The pathology and clinical phenotypes of MA-ILD overlap with other forms of autoimmune ILDs and idiopathic pulmonary fibrosis (IPF). Many MA-ILD patients, similar to autoimmune ILDs and IPF, present with progressive fibrosing phenotype, however, the exact prevalence among patients with MA-ILD is unknown.

There are currently no approved or consensus-driven treatments specifically for MA-ILD, and there is considerable variability in management practices of MA-ILD among rheumatologists and pulmonologists in different regions of the world.

Although various immunosuppressive drugs (e.g., mycophenolate, azathioprine, tacrolimus, and biologic agents like rituximab) are commonly used to treat MA-ILD, the response is unpredictable, variable, and not proven. Some patients are refractory to – or intolerant of – immunosuppressive therapy, while others, require combination therapy with high-dose glucocorticoids leading to many steroid-associated adverse events.

More reliable, effective, better-tolerated therapy would meet a significant unmet need for patients with MA-ILD, especially with a progressive fibrosing phenotype. We believe nintedanib could meet this key need, and below, we describe a well-designed, novel exploratory trial of nintedanib plus standard of care (SOC) versus SOC alone in patients with MA-ILD (MINT Trial).

1.2 Nintedanib Background:

Nintedanib, an intracellular tyrosine kinase inhibitor is approved by several international regulatory bodies to slow the progression of lung fibrosis in patients with idiopathic pulmonary fibrosis (IPF). Subsequently, nintedanib was approved to treat other chronic fibrosing ILDs with a progressive phenotype (PF-ILD), including autoimmune disease associated-ILD. However, in phase III, the confirmatory trial of nintedanib for PF-ILD

(INBUILD Trial), MA-ILD was substantially underrepresented despite 26% of subjects having AILD (most commonly rheumatoid arthritis). Despite its regulatory approval, nintedanib has not been accepted by autoimmune diseases specialists as a viable treatment option for MA-ILD patients due to a paucity of data on safety, tolerability, and efficacy in this unique patient population.

1.3 Study Rationale

Studies suggest that pathophysiological mechanisms that drive fibrosis (and ultimately result in the progressive phenotype) are similar between idiopathic ILD such as IPF and ILD associated with autoimmune disease. The aggregate of trial data for nintedanib supports its efficacy in all forms of progressive fibrosing ILD, whether idiopathic or of known cause (related to the exposure or systemic autoimmunity).

Nintedanib has demonstrated anti-fibrotic, anti-inflammatory, and vascular re-modelling effects in several animal models of fibrosing ILD. The SENSCIS trial, a phase 3 trial of nintedanib in systemic sclerosis-associated ILD (SSc-ILD), demonstrated that immunosuppression and nintedanib could be safely administered together and nintedanib was effective in significantly decreasing the rate of decline of Forced Vital Capacity (FVC) in patients with SSc-ILD, independent of background therapy with mycophenolate.

Recently, a case series reported remarkable improvement in cough, dyspnea, functional level, and pulmonary function tests (PFT) after the addition of an anti-fibrotic agent to immunosuppression in patients with the anti-synthetase syndrome, a subset of MA-ILD (Shen L et al. 2020). Another small case series suggested that nintedanib can improve survival if added to immunosuppression in MA-ILD (Liang et al. Frontier in Medicine 2021). However, these studies are small, retrospective, and uncontrolled and have not been able to change the clinical practice in MA-ILD.

Patients clearly prioritize how they feel and function in their daily lives and MA-ILD patients are no exception. These important outcomes are most commonly captured by patients reporting their perceptions, themselves, via so-called patient-reported outcome measures (PROMS). To date, therapeutic trials in ILD have *never* prioritized PROMS despite the value that patients place on these critical constructs. Living with Pulmonary Fibrosis (L-PF) is a questionnaire developed to assess symptoms, their effects, and the quality of life in patients with any form of pulmonary fibrosis, including MA-ILD. The L-PF questionnaire comprises 44 items: 23 in the Symptoms module and 21 in the Impacts module. Recall for items in the Symptoms module is the past 24 hours while recall for items in the Impacts module is the past week. L-PF yields six scores: 1) L-PF Total; 2) Symptoms Total; 3) Symptoms Dyspnea; 4) Symptoms Cough; 5) Symptoms Energy; and 6) Impacts Total. Domain and total scores range from 0 to 100 with higher scores indicating greater impairment.

Patients with a rare disease such as MA-ILD, are best evaluated, treated, and followed longitudinally by experienced teams at centers of excellence. However, many patients do not have access to such specialty care, and in the midst of a global pandemic, access to such centers is further constrained. Remote, digital monitoring (home spirometry, telemedicine) provides an avenue to deliver comprehensive clinical care and to conduct therapeutic trials for such patients regardless of their geographic location or other travel limitations (e.g. pandemic circumstances). In fact, a research model for remote clinical care and research in patients with IIM has previously been funded by the NIH (PI Rohit Aggarwal, R01, NIH/NIAMS 1R01AR071659 - 01A1) and operationalized through the Myositis Center at the University of Pittsburgh [Myositis Patient centered tele-research (My Pacer)].

This program leverages telemedicine, digital remote monitoring with various devices, certified mobile home research nurses (CMRN), and a central pharmacy to ensure research compliance, quality, and integrity and will provide an outstanding framework from which to launch the MINT trial described below. The My Pacer study successfully recruited more than 200, 385, and 760 subjects remotely in 1 week, 1 month, and 6 months, respectively. We successfully screened 111 patients in My Pacer to reach the study target enrollment of 80; in comparison, a traditional, clinic-based recruitment during the same time frame, screened only 46 patients. Further, the drop-out rate in patients enrolled remotely was 9% as compared to 24% for patients enrolled through the clinic.

Given the success of remote recruitment, retention, and feasibility of study procedures, the proposed MINT trial will have 2 ways of recruitment: a. remotely (novel virtual recruitment from anywhere in the U.S. by the University of Pittsburgh using social media and telemedicine) and b. in person at local clinical trial site (traditional recruitment). However, the study procedures will be mostly remote for both remote and local clinical trial sites with few exceptions. Similarly, this trial will also evaluate the feasibility, reliability, and validity of home spirometry as compared to in lab or clinic spirometry in MA-ILD.

2.0 OBJECTIVES

2.1 Primary Objective:

To assess the effect of nintedanib on preserving L-PF measured symptom levels (cough, dyspnea, energy), impacts of disease, and quality of life in patients with MA-ILD who are also receiving SOC treatment.

2.2 Secondary Objectives:

To assess the feasibility and efficiency of remote patient recruitment, enrollment, screen failure, and dropout rates in progressive MA-ILD.

To assess the agreement between the home and lab-based spirometry in MA-ILD patients.

2.3 Hypothesis

In the patients with MA-ILD on SOC immunosuppression, nintedanib will preserve symptom levels, impacts of disease, and quality of life according to the L-PF.

The study will demonstrate the feasibility of remote recruitment, enrollment, and monitoring in a therapeutic clinical trial. Furthermore, the recruitment, enrollment, and dropout rates will be similar between remote and in-person patients.

There will be a strong agreement between the home and lab-based spirometry in MA-ILD

3.0 STUDY ENDPOINTS

3.1 Primary Endpoint:

Change in L-PF Dyspnea score from baseline to 12 weeks.

3.2 Key Secondary Endpoints:

- Other L-PF scores
    - Change in L-PF Dyspnea score from baseline to week 24
    - Change in L-PF Total score from baseline to 12 and 24 weeks
    - Change in L-PF Symptoms score from baseline to 12 and 24 weeks
    - Change in L-PF Cough score from baseline to 12 and 24 weeks
    - Change in L-PF Energy score from baseline to 12 and 24 weeks
    - Change in L-PF Impacts score from baseline to 12 and 24 weeks
- Change in immunosuppressive (IS) regimen
    - Proportion of patients requiring an increased dose or a change in their glucocorticoid (GC) / immunosuppression (IS) agent for clinical worsening/flare of MA-ILD.
- Lung Function Assessment to be done by in-clinic/lab spirometry (screening - done within screening period), week 12 (within +/- 2 weeks), and week 24 (within +/- 2 weeks).
    - Absolute and relative change in FVC (mL) and FVC (%) from baseline to weeks 12 and 24.
    - Proportion of patients with a relative decline from baseline in FVC (mL) and FVC (%) of ≥10%, ≥7.5%, and ≥ 5% at weeks 12 and 24.

- Proportion of patients with stable (+/- <5%) or improved FVC (≥5, ≥7.5, ≥10%) (mL) and FVC (%) from baseline at weeks 12 and 24.
- Time to FVC (mL) and FVC (%) improvement and decline from baseline by (≥5%, 7.5%, 10%) over 24 weeks.
- Time to progression (defined as a. ≥ 10% decline in FVC (mL) or death or transplant over 24 weeks; b. ILD worsening definition (per protocol) or death or transplant over 24 weeks; c. non-elective hospitalization for ILD worsening/flare or death or lung transplant over 24 weeks)

3.3 Other Secondary Endpoints

- Rate of patient recruitment, enrollment, screen failure, and dropout rates between the local sites (average per site) and the remote site.
- Psychometric properties of home spirometry as compared to clinic/lab-based spirometry.
- Absolute and relative changes in the diffusing capacity of lung for carbon monoxide (DLCO) and FEV1 as well as threshold changes similar to the FVC analysis above.
- Progression free survival
  - CTD-ILD outcome as per OMERACT, which is defined as the occurrence of any of the following: death or lung transplant or FVC ≥10% decline or FVC ≥5% decline with DLCO ≥15% decline evaluated at weeks 12 and 24.
  - Clinical worsening is defined as death, lung transplant, or new/worsening O2 requirement at rest (>2L), or non-elective hospitalization for ILD clinical worsening/flare or ILD worsening definition (per protocol) or out of protocol rescue medication for ILD clinical worsening/flare.
- Steroid use (calculated using prednisone dose equivalents) at weeks 12 and 24
  - Mean and median decrease in glucocorticoid dose
  - Absolute and relative changes in glucocorticoid dose.
  - Area under the curve for cumulative total glucocorticoid exposure.
  - Proportion of patients able to decrease glucocorticoid to 5, 7.5, and 10 mg or less of prednisone equivalent (calculated among patients on doses higher than 5, 7.5, and 10 mg, respectively.).
  - Proportion of patients requiring glucocorticoid (GC) rescue therapy (within protocol) for ILD clinical worsening/flare

  - Proportion of patients requiring IV GC rescue therapy for ILD clinical worsening/flare (results in withdrawal of study drug)

- Change in supplemental oxygen needs from baseline to 12 and 24 weeks (captured via items at the end of the L-PF Symptoms module which do not contribute to any score and the patient reported O2 use)
  - Rest
    - Yes/no
    - Flow rate as a continuous variable
  - Activity
    - Flow rate as a continuous variable

- Overall assessment of change at weeks 12 and 24
  - Patient overall assessment of change (by the patient)
  - Physician assessment of change (by a study investigator)

- Changes in physical activity monitor (step-based and cadence measures)

- Changes in Sit to Stand test

- Change in HRCT chest from baseline (i.e., within 3 months of screening to baseline visit if already done as the SOC, otherwise done during screening period) to 24 weeks (i.e. within +/- 4 weeks of 24 weeks visit) using semi-quantitative and quantitative image based scoring.

- Adverse events (AEs) and tolerance
  - Proportion of subjects who discontinue study drug
  - Patients with any AEs
  - Patients with SAEs
  - Patients with AEs of special interest (gastrointestinal perforation and hepatic injury)

3.4 Exploratory Endpoints:

- Lung Function Assessment to be done by home spirometry (supervised and unsupervised). Home spirometry will meet current ATS guidelines.
  - Absolute and relative change in FVC (mL) and FVC (%) from baseline to weeks 12 and 24.
  - Proportion of patients with a relative decline from baseline in FVC (mL) and FVC (%) of ≥10%, ≥7.5%, and≥ 5% at weeks 12 and 24.
  - Proportion of patients with stable (+/- <5%) or improved FVC (≥5, ≥7.5, ≥10%) (mL) and FVC (%) from baseline at weeks 12 and 24.

  - Time to FVC (mL) and FVC (%) improvement and decline from baseline by (≥5%, 7.5%, 10%) over 24 weeks.
  - Time to progression (defined as a. ≥ 10% decline in FVC (mL) or death or transplant over 24 weeks; b. ILD worsening definition (per protocol) or death or transplant over 24 weeks; c. non-elective hospitalization for ILD worsening/flare or death or lung transplant over 24 weeks)

- Changes in other Patient Reported Outcomes (PROs) and clinical outcomes for myositis and ILD.
  - PROs
    - St. George's Respiratory Questionnaire (SGRQ)
    - PROMIS - physical function 20 (PRO)
    - Myositis Symptoms Monitoring (PRO)
  - Muscle enzymes (CK, Aldolase, AST, ALT)
- Changes in pulse oximetry
- Patient's perspective of the trial

4.0 STUDY DESIGN

4.1 Description of the Study

This is a 12-week, exploratory, multi-center, prospective, randomized, double blind, placebo-controlled trial of nintedanib plus standard of care (SOC) immunosuppression (IS) versus placebo plus SOC IS followed by an additional 12 weeks of open-label nintedanib plus SOC in all subjects.

4.2 Study Schema

We will randomize a total of 70 adult subjects with MA-ILD, 35 in active treatment and 35 in the placebo group, across 11 clinical sites and 1 remote site (the University of Pittsburgh only). The University of Pittsburgh will also serve as a clinical site and the coordinating center. We expect enrollment to be completed within 18 months. The number of patients recruited and enrolled (consented) for screening could be higher, due to screen failures which are estimated to be about 20%.

Note: Patients enrolled and randomized from the 11 clinical sites are referred to as **local site** patients in this protocol, and patients enrolled and randomized from the University of Pittsburgh remote site are referred to as **remote site** patients. Remote patients will be solely managed through the University of Pittsburgh.

Randomization will be 1:1 for nintedanib: placebo and stratified by underlying immunosuppressive therapy (mycophenolate vs. others) as well as local vs remote site. All patients must be on the SOC immunosuppression (IS) at screening as per the protocol and should remain on stable doses throughout the trial. At 12 weeks both arms will receive an additional 12 weeks of nintedanib (150 mg PO Q12 hours, maximum dose of 300 mg a day) through week 24 (final study visit). Dose reduction is allowed as per protocol for the management of tolerability and side effects.

For remote site patients, recruitment will occur via social media through vendors such as SplashClinical, KnowRare, and Power, patient/physician organizations/groups, direct outreach to ILD and myositis centers, and online outreach. Interested patients will be recruited through the study website followed by a prescreening process. Those who qualify through prescreening will be enrolled (consented) for screening. Screening as well as all study visits will be completed by telemedicine, home research nurse visits, home monitoring devices, and testing by outside laboratories or centers.

For local site patients, recruitment of patients will be done conventionally through clinics, clinic referrals, and local registries. Patients who qualify through preliminary screening criteria will be formally screened after signing informed consent and their enrollment eligibility determined. The screening visit can be completed in person at the local site (with the exception of Home Spirometry training and validation which is done remotely using telemedicine) or it can be completed as a combination of in-person and virtual (with the use of telemedicine, home research nurse visits, home monitoring devices and testing by outside laboratories or centers.) or solely virtual.

For patients screened and enrolled at local sites, it is highly encouraged all subsequent scheduled study visits (baseline/visit 1 and visits 2-7) be performed virtually, or at the local site as per preference of the study investigator and subject visits can be performed on site. Some components of the visits that require in-person medical staff involvement, such as blood draws, PFTs, and HRCT chest, local sites will have several options for them to complete these assessments. (See Table 1 below). For example, a patient may go to the local site for a blood draw or have it collected by a mobile research nurse. Or a patient may go to the local site for PFTs/HRCT chest or have it done by a PFT lab or imaging center near their home.

For both remote and local site patients, a 28 days post trial AE monitoring follow-up virtual visit will also be performed. The patient perspective about the trial will be ascertained during that visit.

In addition, a 52 week (+/- 2 weeks) follow up (from baseline visit) phone call to review medications as well as to record and obtain any PFTs, and HRCT chest done as SOC.

All patients who prematurely discontinue trial medication will complete an End of Treatment (EOT) visit and 28-day post trial follow up visit. Safety/tolerability data will be assessed based on screening/baseline to Visit 7 (week 24) or screening/baseline to 28 days post trial follow up visit in case of EOT. Patients who prematurely discontinue trial medication will be asked to remain in the study and to return for regularly scheduled visits until the end of the trial.

Note: The 28 day post trial follow up visit may be concurrent with the regularly scheduled 4 weekly follow up visits in case of EOT.

Similarly, all patients who prematurely withdraw (i.e. discontinue trial medication and withdraw from study participation) will need to complete an Early Termination (ET) visit and a 28 day post-trial follow up visit. Safety/tolerability data will be assessed based on screening/baseline to 28 day post-trial follow up visit in case of ET.

Note: EOT/ET/Unscheduled Visits can be done virtually or in person at the local site as per patient and study investigator preference for local site patients.

Table 1: Summary of the location of assessments for Local Site Patients based on visit type.

Visit Component	**Screening Visit (visit 0), visits 4 and 7**	**Baseline (visit 1) and visits 2, 3, 5, and 6 where assessment is required**	**EOT, ET and Unscheduled (Flare/Rescue/End of Treatment form completed)**
Informed Consent	At Local Site OR Virtual	Not applicable	Not applicable
Brief medical history and physical exam and review of data by study investigator	At Local Site OR Virtual	Virtual	At Local Site OR Virtual
Device training and Study Procedures by SS Data Collection by SS	At Local Site OR Virtual	Virtual	At Local Site OR Virtual
Home Spirometry	Virtual	Virtual	Virtual
Vital Signs - BP, HR, SpO2 Height and Weight	At Local Site OR Virtual	Virtual	At Local Site OR Virtual
Sit to Stand Assessment	At Local Site OR Virtual	Virtual	At Local Site OR Virtual
Physical Activity Monitor: SS instructions	At Local Site OR Virtual	Virtual	At Local Site OR Virtual
Patient Questionnaires/PROs	NOT DONE	Virtual	Virtual
Blood collection for screening and safety labs and research samples. If the safety lab are done as SOC within the study visit window. These will be acceptable.	At Local Site OR Mobile Research Nurse OR Outside Lab* (*only for unforeseen circumstances)	At Local Site OR Mobile Research Nurse OR Outside Lab* *(only for unforeseen circumstances)	At Local Site OR Mobile Research Nurse OR Outside Lab* (*only for unforeseen circumstances)
In-lab/Clinic PFTs: • At screening (if not done as per SOC within 4 weeks prior to the screening visit). • At visit 4 (12 weeks), if not done as SOC within +/- 2 weeks of study visit • At visit 7 (24 weeks), if not done as SOC within +/- 2 weeks of study visit.	At Local Site OR Outside PFT lab (near patient home)	At Local Site OR Outside PFT lab (near patient home)	At Local Site OR Outside PFT lab (near patient home)
HRCT Chest: • At screening (if not done as per SOC within 12 weeks prior to the screening visit). • At Visit 7 (week 24) (if not done as SOC within +/- 4 weeks of visit date)	At Local Site OR Outside radiology imaging center (near patient home)	At Local Site OR Outside radiology imaging center (near patient home)	At Local Site OR Outside radiology imaging center (near patient home)

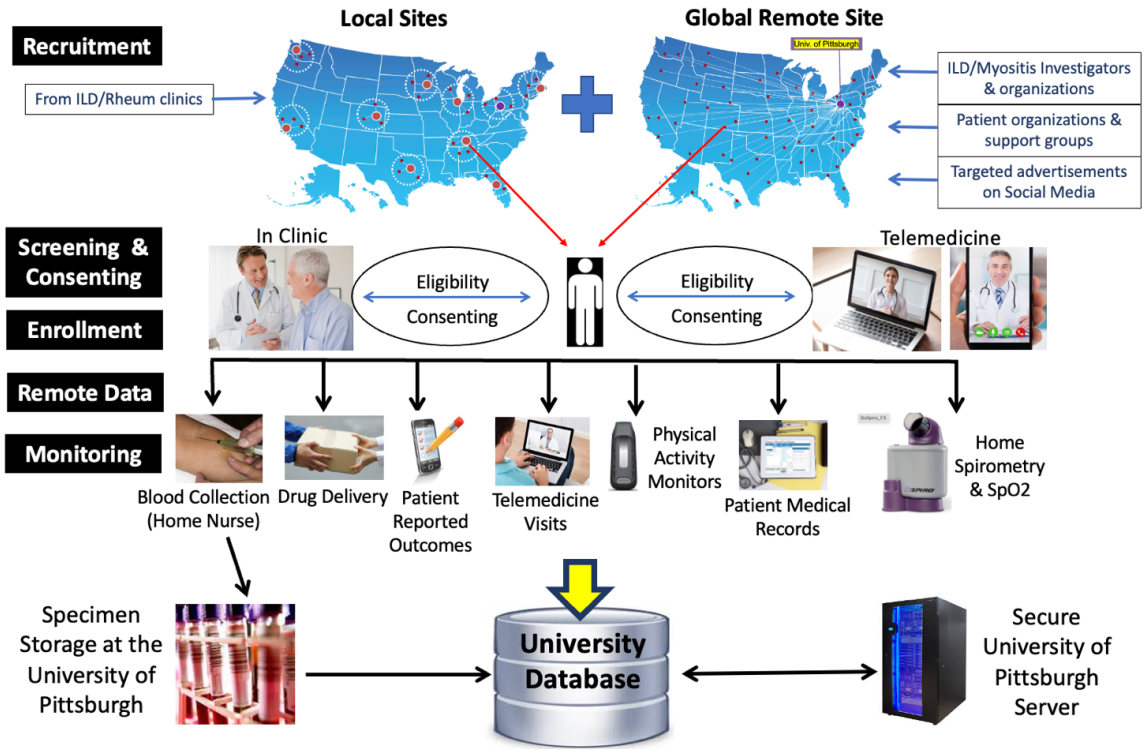
Note: Prescreening activities for local site patients can be done in person or on the phone or telemedicine in conjunction with the review of medical records.

*screening visits, EOT, ET, and unscheduled visits can be done either in-person at the local site, or virtual (telemedicine) or by a combination of in-person at the local site and virtual (telemedicine).

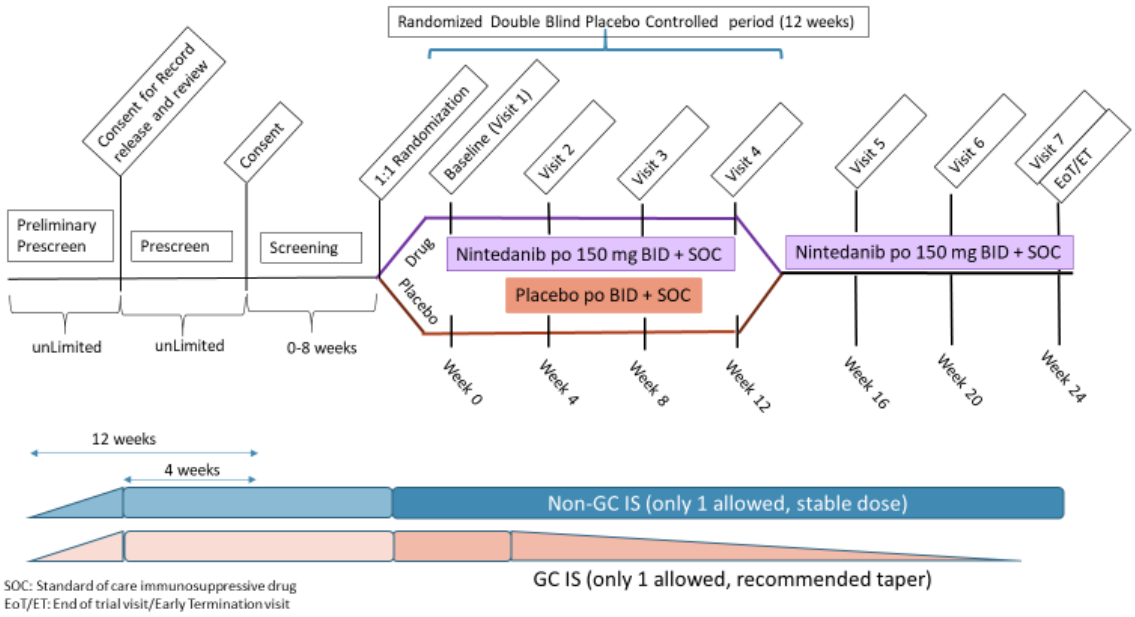
The primary analysis of this study will be performed once the last randomized patient reaches 12 weeks, at which time the first database lock will occur and all data up to 12 weeks will be unblinded. The final analysis of this study will be performed once the last randomized patient reaches 24 weeks, at which time the final database lock will occur.

A Data Safety Monitoring Board, independent of the investigatory team, will monitor and assess the progress of the clinical trial, including safety assessments at specified intervals. An independent medical monitor, will be responsible for ensuring all required activities are as per applicable regulations and standard operating procedures (SOP)s as well as directing the coordinating team regarding the conduct and reporting of the trial.

4.3 Flow Diagram of the Clinical Trial Process



4.4 Study Design Diagram



4.5 Biobank

Serum samples for research will be collected from patients and stored at the University of Pittsburgh Research Laboratory in the Division of Rheumatology and Clinical Immunology, Department of Medicine. Samples will be used at a later date (after additional funding is acquired) to evaluate novel biomarkers to understand the effects of nintedanib on myositis-associated ILD patients and identify predictive factors of safety, tolerability, or response to a combination of nintedanib and immunosuppression.

All biospecimens will be collected and stored in accordance with the protocol. During the course of the trial, Boehringer Ingelheim (BI) is authorized to use the biospecimens in any manner consistent with the terms of the informed consent form and all applicable laws, rules, or regulations. Use of the biospecimens requires approval by steering committee and BI. At trial completion, the use of the biospecimens shall be subject to the mutual agreement of the parties.

4.6 Other Considerations

HRCT chest: In addition to reports of HRCT chest imaging, the images stored on a CD or in the EMR should be reviewed and scored by the site study investigators on the HRCT chest form. In addition, de-identified images of the chest HRCTs will be collected

by the coordinating center for future exploratory analysis using quantitative and semi-quantitative scoring.

Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire (L-PF): The Living with Pulmonary Fibrosis (L-PF) questionnaire is a 44-item questionnaire with two modules: 1) symptoms (23 items) and 2) impacts (21 items). L-PF was developed with the input of patients with pulmonary fibrosis (PF) and thus is intended to capture perceptions specific to PF patients. The Symptoms module yields three domain scores: 1) dyspnea, 2) cough and 3) fatigue as well as a total Symptoms score. The Impacts module yields a single Impacts score. Symptoms and Impacts scores are summed to yield a total L-PF score. Scoring is performed as a summary score with the mean of the dimension ratings multiplied by 100. Summary score range from 0-100, the higher the score the greater the impairment.

The L-PF Symptoms and Impact Questionnaire will be self-administered by the patient at visits indicated in the study schema via the study tablet.

Spirometry assessment of FVC (In lab/clinic as well as home): Spirometry measurements must be performed according to the 2019 update to the ATS/ERS guidelines. Spirometry will be conducted while the patient is in a seated position. The test will be done in triplicate (three curves to be provided), and the best result selected according to the guidelines. The best of three efforts will be defined as the highest FVC, obtained on any of the three blows meeting the ATS/ERS criteria with a maximum of 8 maneuvers. Efforts should be made to schedule the spirometry measurements at approximately the same time of the day, with reference to the baseline measurement. On days of study visits, patients must refrain from strenuous activity at least 1 hour before pulmonary function testing (home or in clinic/lab spirometry). Smoking should be discouraged throughout the visit days (clinic visit) and will not be permitted in the 60 minutes before spirometry. Patients should also avoid cold temperatures, environmental smoke, dust, or areas with strong odors (e.g. perfumes). If treated with bronchodilators, a 24 hour wash-out period for long acting and 8 hours for short acting bronchodilators should be observed before spirometry.

Spirometry results will be electronically transmitted. To ensure the quality of measurements, a central spirometry review is in place to provide feedback to PFT technicians.

DLCO (Diffusing Capacity for Carbon Monoxide): For predicted normal values, different sites/centers/PFT labs may use different prediction formulas, based on the

method used to measure DLCO. In any case, the method used must comply with the ATS/ERS guidelines on DLCO measurements with the prediction formula appropriate for that method.

Percent predicted DLCO corrected for hemoglobin (Hgb) expressed in g·dL-1 can be calculated as:

- Male: Percent predicted DLCO corrected for Hgb = Percent predicted DLCO x (10.22+Hgb)/(1.7Hgb) for males
- Female: Percent predicted DLCO corrected for Hgb = Percent predicted DLCO x (9.38+Hgb)/(1.7Hgb) for females

5.0 SUBJECT SELECTION

Overview: 134 adult subjects ≥ 18 years with MA-ILD will be enrolled and randomized. Note approximately 20% more patients will be enrolled (consented) for screening due to the expected screen failure rate of 20%.

5.1 Eligibility Pre-Screening

All patients from both remote and local sites will undergo pre-screen before being approved for a screening visit.

The pre-screening process for remote site patients includes a preliminary pre-screening questionnaire, pre-screening consent, release of medical information, collection of contact information, local treating physician approval, and preliminary eligibility form and review.

The pre-screening process for local site patients includes collection of contact information and a pre-screen form and review. In addition, if the patient is not being seen clinically at the local site (i.e., the patient does not get clinical care at the center), then prescreening consent, the release of medication information, and local treating physician approval are also required.

Local treating physician approval: A study investigator will contact the patient's treating myositis/ILD health care provider via email or phone call to discuss the patient's eligibility as well as study plans and ultimately will seek local physician approval for the trial contingent on the patient passing the screening criteria. The local treating physician's approval will be documented. This approval is not required for local site patients if the patient is clinically being seen at the local site (i.e. patient gets clinical care from the center).

Preliminary Eligibility Review: A Study investigator will review the medical records and prescreening data and will discuss with the patient's myositis-ILD physician (if needed) to determine preliminary eligibility.

5.2 Study Consent

Once the patient has been determined to have preliminary eligibility for the study, full study consent will be obtained before proceeding to the screening visit and all other study procedures. Consent is addressed further in Enrollment and Study Visit sections.

5.3 Inclusion and Exclusion Criteria

The following will be assessed during the screening period based on data obtained during the preliminary eligibility review and patient assessments and labs/tests completed during the screening period.

5.3.1 Inclusion Criteria

1. Subject has provided written informed consent
2. Approval from local treating physician (done at pre-screening only for remote patients as well as for local site patients not actively being managed at the local site).
3. Subject lives in the United States
4. Adult: Age ≥ 18 years
5. Subject can speak, read, and understand English or Spanish
6. Subject is willing and capable of performing all study procedures.
7. Validity/repeatability of home spirometry confirmed by PFT lab technician/study investigator through telemedicine as per ATS guidelines.
8. Men and women of reproductive potential must agree to use 2 reliable methods of birth control during the trial period.
9. Clinical diagnosis of myositis or presence of one of the following myositis-specific or -associated autoantibodies).
    a. Anti-synthetase autoantibody (Anti-Jo-1, -PL-7, -PL-12, -EJ, -OJ, -KS, -Tyr, -Zo)
    b. Anti-MDA5, TIF1-gamma, Mi-2, NXP2/MJ, SAE, HMGCR, SRP
    c. Anti-PM/Scl, Ku, U1RNP, Ro5,2/60, or SSA (in absence of clinical diagnosis of systemic sclerosis or primary Sjogren syndrome).
10. Fibrosing Interstitial Lung Disease (ILD):

a) HRCT chest within 12 months of screening visit with fibrosing ILD (reticular changes, traction bronchiectasis, and/or honeycombing)

b) No other identifiable cause of fibrosis

c) The following co-existing features are expected and accepted: ground glass opacity, upper lung or peri-bronchovascular predominance, mosaic attenuation, air trapping, consolidation, and centrilobular nodules.

11. Progressive ILD: Defined as meeting ≥1 of the following criteria within 24 months of the screening visit.
    a. ≥10% relative decline in FVC% predicted (%pred)
    b. ≥5 but <10% relative decline in FVC %pred with worsening dyspnea.
    c. ≥5 but <10% relative decline in FVC %pred with worsening chest HRCT fibrotic changes
    d. Worsening dyspnea with worsening chest HRCT fibrosis
    e. Worsening dyspnea with FVC% <= 70%
12. Standard of care (SOC) therapy: (See: SOC immunosuppression and washout under section 6.2 for details)
    a. Allowable SOC includes a maximum of 3: 1 glucocorticoid (GC) and 2 Non-GC immunosuppressive medication (IS) Or 3 Non-GC immunosuppressive medications.
    b. Allowable IS component of SOC regimen must have been started at least 12 weeks prior and be stable for at least 4 weeks before baseline visit.
    c. In case a patient is not on any of the SOC immunosuppression, patient can be enrolled if at least 2 SOC immunosuppression are either previously failed or had intolerance or are contra-indicated.
    d. Allowable GC component of SOC regimen must have been started at least 4 weeks prior and be stable for at least 2 weeks before baseline visit.
    e. Allowable IS and GC:
        i. Glucocorticoid (maximum dose ≤20 mg/day; prednisone equivalent).
        ii. Mycophenolate mofetil (max dose 3 gm/day)
        iii. Mycophenolic acid (max dose of 2,160 mg/day)Azathioprine (max dose 2.5 mg/kg/day)
        iv. Methotrexate (max dose 25 mg/week)
        v. Tacrolimus (max dose 10 mg/day)

vi. Cyclosporine (max dose 200 mg/day)

vii. Leflunomide (max dose 20 mg/day)

viii. Sulfasalazine (max dose 3 gm/day)

ix. JAK inhibitors (tofacitinib max dose 11 mg/day, upadacitinib max dose 15 mg/day, baricitinib max 4 mg/day)

x. IVIG (Intravenous immunoglobulin) or SQIG (subcutaneous immunoglobulin) (max dose 2 gm/kg/month) is allowed and not considered as SOC IS therapy

xi. Rituximab (maximum dose 1000 mg x 2 (2 weeks apart) or 375mg/m^2 weekly dose x 4, repeated every $\geq$ 4 months)

xii. Hydroxychloroquine is allowed and not considered as SOC IS therapy

xiii. Orencia (maximum dose of 125 mg SQ once a week or 1 gm monthly IV infusion).

f. Inhaled medication(s) for lung disease is allowed if started > 4 weeks before screening. Should remain stable throughout the study.

13. Negative pregnancy test

5.3.2 Exclusion Criteria

1. Planned major surgical procedures within the trial period of 24 weeks.
2. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
3. Women of childbearing potential* not willing or able to use at least two highly effective methods of birth control.

    a. For females of reproductive potential: use of highly effective contraception for at least 1 month before study drug administration and agreement to use such a method during study participation and for an additional 3 months after the end of study drug administration.

    b. For males of reproductive potential**: use of condoms or other methods to ensure effective contraception with a partner

    Highly effective contraception examples are:

    • An approved hormonal contraceptive such as oral contraceptives, emergency contraception used as directed, patches, implants, injections, rings, hormonally-impregnated intrauterine device (IUD), or nonhormonal IUD

    • Abstinence

• Condoms

* A woman is considered of childbearing potential, i.e. fertile, following menarche, and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, tubal occlusion, and bilateral oophorectomy.

**A man is considered permanently sterile if a vasectomy has been performed

4. Severe lung disease is defined by the following within the last 6 months before the screening:
    a. FVC ≤40 percent predicted
    b. DLCO <30% of percent predicted (corrected for Hb)
    c. O2 requirement of ≥10 L at rest based on home oxygen prescription.
    d. Patient listed for lung transplant or actively going through lung transplant evaluation.
5. Moderate to severe active muscle disease from myositis as per any one of the criteria:
    a. Creatine kinase (CK) > 2000 U/mL.
    b. Moderate to severe dermatomyositis rashes as per a study investigator evaluation (if rash present)
    c. Moderate to severe arthritis as per a study investigator evaluation
    d. Moderate to severe muscle weakness as per Sit to Stand 30 seconds of < 7.
6. History of or ongoing serious active, chronic, or recurrent infection within 4 weeks of screening
7. Significant Pulmonary Hypertension (PH) is defined by any of the following:
    a) Current clinical diagnosis of moderate to severe PH or significant right heart failure.
    b) History of echocardiographic evidence of significant right heart failure or moderate to severe PH (TR jet >= 2.9 m/s and signs of RV dysfunction; or TR jet > 3.4; or an RVSP > 40-55 with evidence of RV strain or dysfunction; or RVSP > 55 regardless.
    c) History of right heart catheterization showing a cardiac index ≤ 2.2 l/min/m² or mPAP >40mmHg with a PCWP <15mmHg
    d) PH requiring oral, IV, or inhaled therapy (such as epoprostenol, treprostinil, iloprost, bosentan, ambrisentan, sildenafil, and tadalafil).
8. Increased bleeding risk, defined by any of the following:
    a. Patients who require

i. Fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, factor Xa inhibitors, low molecular weight heparin)

ii. High dose antiplatelet therapy (>325mg acetylsalicylic acid or >75mg clopidogrel).

b. History of hemorrhagic central nervous system (CNS) event within 12 months of screening.

c. Any of the following within 3 months of screening:

i. Hemoptysis or hematuria

ii. Active gastrointestinal (GI) bleeding or active GI ulcers.

d. Coagulation parameters: International normalized ratio (INR) >2, prolongation of prothrombin time (PT) and by >1.5 x ULN at screening.

9. History of a thrombotic event (including stroke and transient ischemic attack) within 12 months of screening.
10. Severe Cardiovascular disease, any of the following:
    a. Severe hypertension, uncontrolled under treatment (≥160/100 mmHg), within 6 months of screening.
    b. Myocardial infarction or unstable cardiac angina within 6 months of screening.
11. Patients with underlying chronic liver disease (Child-Pugh A, B, or C hepatic impairment).
12. Known hypersensitivity to the trial medication or its components (i.e. soya lecithin)
13. Other diseases that may interfere with testing procedures or in the judgment of the study investigator may interfere with trial participation (such as significant GI issues like irritable bowel syndrome, inflammatory bowel disease, recent abdominal surgery, diverticular disease), or significant other lung diseases (such as severe obstructive lung disease such as severe asthma or severe chronic obstructive pulmonary disease, etc.) or may put the patient at risk when participating in this trial.
14. Life expectancy for a disease other than ILD < 2.5 years (study investigator assessment).
15. In the opinion of a study investigator, any condition precluding participation and completion of the study, including active alcohol and drug abuse or patients not able to understand or follow trial procedures.
16. Other investigational therapy was received within 1 month or 6 half-lives (whichever was greater) before the screening visit.

17. Current treatment with nintedanib or pirfenidone (taken the drug within 3 month of randomization or history of intolerance/side effects)
18. Current or recent use of one or more of the following medications (See: SOC immunosuppression and washout under section 6.2 for details)
    a. Cyclophosphamide within 3 months of baseline.
    b. Anti-TNF (infliximab, golimumab, or certolizumab) within 8 weeks or adalimumab within 4 weeks, and etanercept within 2 weeks of baseline.
    c. Anakinra within 1 week of baseline.
    d. Other biological agents such as tocilizumab, etc. within 4 weeks of baseline.
19. Safety laboratory abnormality as any one of below
    a. AST, ALT > 1.5 x ULN at screening, unless deemed due to active myositis by investigator, in which case CK is also abnormally elevated and the ratio of AST or ALT by CK levels (adjusted as x ULN) should be < 2.0 and GGT < 2.0 x ULN.
    b. Bilirubin > 1.5 x ULN at screening
    c. Creatinine clearance <30 mL/min calculated by Cockcroft–Gault formula at screening.
    d. Hgb < 9.0
    e. Platelet count < 100,000/mm3
    f. White blood cells < 3000/mm3

Note: PT/INR is also screening labs which are assessed as part of exclusion criteria # 8d above.

Footnote: Creatinine clearance calculation is done according to Cockroft and Gault. Creatinine clearance = (140 - age) x (Weight in kg) x (0.85 if female) / (72 x serum creatinine in mg/dL)

5.4 Immunization during Nintedanib therapy

There is no contraindication to receiving live vaccines with nintedanib as it is not an immunosuppressive drug.

6.0 STUDY INTERVENTION / INVESTIGATIONAL AGENT

6.1 Description

Nintedanib is an intracellular inhibitor of multiple receptors and non-receptor tyrosine kinases.

6.2 Treatment Plan Dosing/Regimen and Administration

Two Arms:

- Nintedanib 150mg BID + SOC Immunosuppressive Therapy for 12 weeks
- Placebo BID + SOC Immunosuppressive Therapy for 12 weeks.
- Followed by open-label nintedanib 150mg BID + SOC Immunosuppressive Therapy for additional 12 weeks for all patients.

Nintedanib: 150 mg oral BID with optional dose reduction to 100 BID (200 mg total daily dose) to manage adverse events. Nintedanib dose adjustment regimen for adverse event management: Dose reduction (150 mg bid to 100 mg bid) or temporary treatment interruption or adverse event management (see adverse event management plan) should be considered to manage adverse events. No further dose reduction below 100 mg bid is allowed. In case of adverse events observed at this reduced dose despite attempts to manage adverse events, permanent treatment interruption should be considered. Treatment interruption, reduction, and re-increase are allowed on multiple occasions.

Placebo: A matching placebo will be developed by the drug company in the same packing and label.

Trial Medication Intake: Trial medication is self-administered. It is to be taken with a glass of water (~250 mL) and should observe a dosing interval of 12 hours. The patients should swallow the trial medication with water without chewing. Trial medication needs to be taken at the same time every day (between 06:00 and 11:00 in the morning, and between 6:00 and 11:00 p.m.). Because nintedanib may cause stomach discomfort, it is recommended to take the trial medication after food intake. A forgotten dose should be skipped if the time window to the next dose is less than 8 hours. The following dose should be taken according to the protocol. No catch-up of missed doses is permitted.

Study drug accountability and dispensing will be coordinated through a central pharmacy. The drug will be dispensed in bottles with 30 tablets each on a monthly basis, (2 bottles every 4 weeks over a 24-week timeframe). The study drug will be shipped via a specialty courier directly to the subject's home within 5 days after the baseline visit (post randomization). The 30 days (2 bottles, 60 tablets) supply of the study drug will be securely stored by the subject in a study provided pill box and administered twice a day. If at any point the subject's dose is reduced to 100 mg BID, the central pharmacy will ship 100 mg pills directly to the subject's home. No temperature monitoring is required. At each study visit, the study staff (SS) will perform a visual inventory of the study drug

via telemedicine and complete the patient drug accountability form. Within the monthly shipment of each study drug box, the central pharmacy will provide instructions to return empty drug bottles from the previous month. In the case of early discontinuation of the study drug, the remaining drugs will be shipped back to the central pharmacy for drug accountability.

The central clinical pharmacy will maintain a record of the product's delivery and inventory from the sponsor to the central pharmacy and from the central pharmacy to each patient as well as the return to the sponsor or disposal of unused products. These records will include dates, quantities, batch/serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational product and trial patients. The central clinical pharmacy will maintain records that document adequately that the patients were provided the doses as per trial specifications and reconcile all investigational products received from the sponsor. At the time of return to the Sponsor, the central pharmacy must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the patient's possession.

SOC Immunosuppressive (IS): Maximum of 3 SOC IS drugs are allowed, one being a glucocorticoid (GC) and the others being a non-GC IS drugs OR 3 non-GC IS drugs in the event that the patient is not on a GC). The patient should be on the IS drug(s) for at least 12 weeks (at least 4 weeks or more for GC) before the baseline visit. The doses should be stable for at least 4 weeks (at least 2 weeks for GC) before the screening visit.

i. Glucocorticoid (maximum dose ≤20 mg/day; prednisone equivalent).

ii. Mycophenolate (max dose of 3 gm/day)

iii. Azathioprine (max dose of 2.5 mg/kg/day)

iv. Methotrexate (max dose of 25 mg/week)

v. Tacrolimus (max dose of 10 mg a day)

vi. Cyclosporine (max dose of 200 mg a day)

vii. Leflunomide (max dose of 20 mg a day)

viii. Sulfasalazine (max dose of 3 gm/day)

ix. JAK inhibitors (tofacitinib max dose 11 mg/day, upadacitinib max dose 15 mg/day, baricitinib max 4 mg/day)

x. IVIG (Intravenous immunoglobulin) or SQIG (subcutaneous immunoglobulin) (max dose of 2 gm/kg per month) is allowed and not considered as SOC IS therapy

xi. Rituximab (maximum dose 1000 mg x 2 (2 weeks apart) or 375mg/m^2 weekly dose x 4, repeated every $\geq$ 4 months)

xii. Orencia (maximum dose of 125 mg SQ once a week or 1 gm monthly IV infusion)

xiii. Hydroxychloroquine is allowed and not considered as SOC IS therapy.

Washout for IS and GC: If the enrolling study investigator is planning to discontinue any IS or GC before the clinical trial, then at least the following washout period is required before the baseline visit.

Medication	**Washout Period**
Methotrexate	4 weeks
Other IS agent (e.g. azathioprine, cyclosporine, tacrolimus, leflunomide, mycophenolate mofetil)	4 weeks
Cyclophosphamide	12 weeks
IVIG/SQIG	4 weeks
Infliximab or Golimumab, Certolizumab	8 weeks
Glucocorticoids (GC)	2 weeks
Etanercept or Abatacept, tocilizumab, other biologics	2 weeks
Adalimumab	4 weeks
Anakinra	1 week
JAK inhibitors (tofacitinib, upadacitinib, baricitinib, others)	4 weeks

Note: Use of P-glycoprotein (P-gp) and/or CYP3A4 inhibitors/inducers known to affect nintedanib pharmacokinetics (not limited to the following) must be washed out 4 weeks before baseline.

a. Ketoconazole

b. Erythromycin

c. Rifampicin

d. Carbamazepine

e. Phenytoin

f. St. John's wort

Recommended Tapering of Oral Glucocorticoids (GC) from weeks 4 to 20. GC dose should be tapered as per recommended GC taper given below starting 4 weeks after baseline to 4 weeks before week 24 visit. No GC dose changes are allowed in the first 4 weeks and last 4 weeks of the trial. Faster tapering or stopping of GCs is permitted after discussion with a medical monitor for safety and tolerability reasons. All changes in GC dose should be documented.

All doses are in prednisone equivalent. Note that the holding of the recommended GC taper is allowed at any time as per the treating study investigator for a maximum of 4 weeks per episode/request after which recommended GC tapering should resume from the level at which it was held. The treating study investigator can hold GC tapers for any number of times/episodes (4 weeks each), and each time should be documented.

- 15-20 mg: Decrease by 2.5 mg every 2 weeks. If starting dose is 19 or 18 mg, then the first decrease will be to 17.5 mg a day at 2 weeks. If starting dose is 16 or 17 mg, then the first decrease will be to 15 mg a day at 2 weeks.
- 10-15 mg: Decrease by 2.5 mg every 2 weeks. If starting dose is 13 or 14 mg, then the first decrease will be to 12.5 mg at 2 weeks. if the starting dose is 11 or 12 mg, then the first decrease will be to 10 mg at 4 weeks.
- 5-10 mg: Decrease by 1 mg every 2 weeks. If starting dose is 7.5 mg, then the first decrease will be to 7 mg at 4 weeks.
- 5 mg or less: No taper recommended by trial, but can be tapered as per treating study investigator.

Note: First time-point at which the dose will be decreased as per the above protocol is at 4 weeks from baseline. The last time point at which the dose will be decreased as per the above protocol is at 20 weeks from baseline. **The treating study investigator can hold GC tapers for any number of times/episodes (4 weeks each), and each time should be documented and taper resumes after 4 weeks.**

Change in Immunosuppression (non-GC IS) NOT allowed: Permitted immunosuppressive (IS) medications should be kept at a stable dose, and no changes in non-GC IS medication or doses are allowed throughout the clinical trial. A decrease in dose or temporary holding or change of SOC IS (or incorrect dose taken due to patient error with subsequent correction) may be allowed to maintain patient safety or tolerability-based on discussion with – and the permission of – the medical monitor. All changes and reasons should be documented in the Flare/Rescue/End of Treatment form.

A patient requiring a change in IS, the addition of IS (whether allowable or not), or an increase in the dose of IS for management of myositis or ILD progression is considered as a non-responder (considered as out of protocol rescue) and will continue to receive trial drug unless the IS regimen is not consistent with the inclusion criteria such as > 2 IS/GC or non-allowable IS, etc. (see trial drug stopping rules section 10.1 and Appendix A). However, all attempts will be taken to keep the patient in the trial for monitoring, even if the patient comes off the trial drug.

Increase of systemic oral glucocorticoids (GC) is ONLY allowed as a rescue therapy: No increase in GC dose above baseline dose (or new GC start if the patient was not on GC at baseline) is allowed unless being used as rescue therapy (See rescue therapy plan). All changes and reasons should be documented before/at the time of change in the Flare/Rescue/End of Treatment form. Any patient who receives high doses of GC (> 1 mg/kg prednisone dose equivalent for > 3 days) for ILD progression will be considered a non-responder and will be withdrawn from the trial drug. However, all attempts will be taken to keep the patient in the trial for monitoring, even if the patient comes off the trial drug. Otherwise, if a patient receives out of protocol GC (> 1 GC rescue required or out of protocol GC except for high dose GC (as defined above), the patient will be considered a non-responder and will NOT result in the subject being withdrawn from the trial drug (see trial drug stopping rules section 10.1 and appendix A). A decrease in dose or temporary holding of GC other than the GC taper (or incorrect dose taken due to patient error with subsequent correction) may be allowed to maintain patient safety or tolerability, based on discussion with – and the permission of – the medical monitor. Similarly, a temporary increase in GC for non-myositis or ILD reasons such as contact skin allergy (poison ivy) or asthma attack or other reasons with subsequent return to GC dose as per trial, may be allowed based on discussion with the medical monitor.

Inhaled medications: Inhaled medication(s) for lung disease should remain stable throughout the study unless as per an allowable rescue plan or for patient safety or as deemed medically necessary after discussion with the medical monitor.

All the changes in GC/non-GC IS or any disease specific medication(s) are to be documented in the Flare/Rescue/End of Treatment form.

6.3 Definitions of Worsening Criteria

Meeting “worsening criteria” does not automatically mean the administration of rescue therapy. Rescue therapy is given if the treating physician believes the clinical disease

warrants a change in therapy (with or without meeting worsening criteria). Subjects meeting these criteria can continue to receive the study drug if deemed reasonable by the study investigator. See rules for stopping the trial drug (section10.1) based on rescue medication used by the treating physician as well as Appendix A (Clinical Worsening/Flare Up Flow Chart).

Flare is defined as a significant clinical worsening of the disease as reported by the patient and/or their treating physician and/or study investigator. Note: Flare or clinical worsening may or may not meet worsening criteria (myositis and/or ILD).

For the clinical trial, the flare has to be confirmed by the site study investigator or have to a change in treatment (to be documented on the Flare/Rescue/End of Treatment form).

6.3.1 Myositis Worsening Criteria

If the below criteria are met after 4 weeks of therapy (at visit 1 or onwards):

- Moderate to severe worsening as per study investigator assessment AND one of the following:
  a. Worsening of Sit to Stand by ≥ 3 repetitions (a surrogate for worsening muscle weakness).
  b. Moderate to severe worsening of DM-related rash or arthritis as compared to baseline (per study investigator assessment)

Note: SS should also **complete the Flare/Rescue/End of Treatment form.**

Note that meeting "worsening criteria" does **not** mean rescue therapy must be administered. Rescue therapy is given only if the treating physician/study investigator believes it is clinically warranted (with or without meeting worsening criteria). Moreover, subjects meeting these criteria can continue to receive the study drug if deemed reasonable by the study investigator.

6.3.2 ILD Worsening Criteria

If any one of the below criteria is met after 4 weeks of therapy (at visit 1 or onwards):

a. FVC% decline ≥ 30% from baseline PFT

b. HRCT chest suggesting severe worsening in the ILD as compared to baseline (clinician/radiologist interpretation)

c. Hospitalization with severe ILD with new O2 requirement related to worsening ILD

d. Severe worsening in clinical dyspnea due to ILD as determined by the patient and treating physician.

Note: SS should also **complete the Flare/Rescue/ End of Treatment form.**

Note that meeting "worsening criteria" does **not** mean rescue therapy must be administered. Rescue therapy is given only if the treating physician/study investigator believes it is clinically warranted (with or without meeting worsening criteria). Subjects meeting these criteria will be considered treatment failures (non-responder) but can continue to receive study drug if deemed reasonable by the study investigator.

6.3.3 Non-Responder

Patients meeting ILD worsening criteria or requiring out of protocol rescue for ILD worsening will be considered non-responders (treatment failures). However, if the change is due to safety or tolerability or other reasons, then patient is not automatically designated as non-responder. The non-responder status will be used for sensitivity analysis for all outcome measures, where the non-responder status will be considered as a negative outcome for a categorical outcome and data censored at the time of non-response status for continuous outcomes. An unscheduled visit should be conducted at the time of ILD worsening or requiring out-of-protocol rescue for ILD worsening if it is not within +/- 1 week of a regularly scheduled visit.

6.4 Rescue Medications

If in the clinical site study investigator's opinion there are complications or worsening of disease (with or without meeting formal worsening criteria as above) that necessitate an increase or change in ILD/myositis disease-specific medication(s) such as an increase in concomitant immunosuppressive therapy, the below guidelines should be followed. SS should also complete the Flare/Rescue/End of Treatment form.

Allowable Rescue therapy plan:

Any one or more of the following is allowed simultaneously or at different time points as protocol rescue therapy. *The exception is oral/inhaled GC rescue, which is allowed only once.*

- Hydroxychloroquine (HCQ) can be started or the dose increased up to 400 mg per day (maximum dose is 5 mg/kg or 400 mg whichever is lower)
- Topical or oral non-steroidal anti-inflammatory agents
- Pain (non-narcotic, and not controlled substances) or pruritus medications
- Intra-articular or intra-bursal GC injections

- Topical GC (medium potency) or topical tacrolimus
- Oral/inhaled GC rescue therapy plan as below.

Oral/Inhaled GC rescue therapy plan: Any one (and only one) of the below GC rescue plans are allowed for ILD or non-ILD clinical worsening (with or without meeting formal worsening criteria) up to 1 time during the clinical trial and should be documented in the Concomitant Medication and Steroid Taper forms as well as **Flare/Rescue/End of Treatment form**. This will NOT constitute a non-responder. However, any oral GC rescue above and beyond the allowable plans below, such as high dose GC (>1 mg/kg daily dose prednisone equivalent) or requiring rescue plan > 1 time, or IV GC for clinical worsening, will result in the patient being considered as a non-responder. Patients in such situations can continue to receive trial drug if deemed reasonable by the study investigator and as per the stopping rules (Section 10.1, Appendix A). Also, in all such circumstances, the patient will be continued to be followed per the protocol and all study procedures will be followed except for procedures specifically related to study drug intake in case the study drug is stopped by the study investigator or the patient.

- Increase in oral GC dose up to baseline dose (dose at Week 0). Subjects should thereafter directly follow the recommended GC taper schedule after 2 weeks.
- Increase in oral GC dose up to 20 mg per day (if baseline dose at Week 0 was less than 20 mg/day). Subjects should thereafter directly follow the protocol-defined GC taper schedule after 2 weeks.
- Oral GC taper of 20 mg per day of prednisone (or equivalent) over 4 weeks can be given in addition to the baseline GC dose. Adding prednisone (or equivalent) 20 mg per day for one week, then 15 mg per day for one week, then 10 mg per day for one week, then 5 mg per day for one week, then back to baseline GC dose.
- New or increase in dose/frequency of inhaled GC alone or in combination with another inhaled drug.

6.5 Nintedanib Dose Modification and Toxicity Management

Table 2: Allowed treatment interruption/dose reduction periods:

	AEs considered related to study drug	AEs not considered related to study drug
Maximum interruption	4 weeks	4 weeks
Recommended restart	With reduced dose of 100 mg BID	With the same dose as before interruption

		(100 mg bid or 150 mg bid)
Re-escalation is optional	Within 4 weeks to 150 mg bid	NA

Management of diarrhea

Diarrhea is a known side effect of nintedanib treatment. However, potential causes for diarrhea other than study medication should always be considered and treated accordingly (e.g. viral infections, bacterial overgrowth, antibiotic treatment). If felt to be non-infectious and related to the study drug, diarrhea should be managed as early as possible after the onset of first symptoms with standard anti-diarrheal symptomatic treatment, e.g. loperamide. If diarrhea persists despite optimal symptomatic treatment, treatment interruption and/or dose reduction of nintedanib to 100 mg bid should be considered according to the recommendations described in Table 3 below.

Table 3: Management of diarrhea

Description	Symptomatic Treatment	Action with trial medication
Diarrhea with increase of <4 stools per day over baseline*.	Initiate anti-diarrheal medicines at first signs of symptoms (e.g. 4 mg loperamide followed by 2 mg after each loose stool or every 2-4 hours to a maximum of 16 mg/day) until bowel movements cease for 12 hours. Advise adequate fluid take.	Continue same trial medication dose.
Diarrhea with increase of 4 to 6 stools per day over baseline*.	Initiate/continue anti-diarrheal medicines as above. If diarrhea of this severity persists for ≥48 to 72 hours assess for dehydration and electrolyte imbalance by doing labs and/or unscheduled visits assessment. Further management as clinically indicated.	If diarrhea persists for ≥48 to 72 hours despite optimal symptomatic care: 1. Interrupt trial medication until recovery. 2. Reduce dose to 100 mg bid after recovery. 3. Re-escalate to 150 mg bid within 4 weeks if deemed clinically appropriate.
Diarrhea with increase of ≥7 stools per day over baseline* or stool incontinence.	Initiate/continue anti-diarrheal medicines as above. Assess for dehydration and electrolyte imbalance by doing labs and/or unscheduled visits assessment. Further management as clinically indicated.	1. Interrupt trial medication until recovery. 2. Reduce dose to 100 mg bid after recovery. 3. Consider re-escalation within 4 weeks to 150 mg bid if deemed clinically appropriate. 4. In case of reoccurrence of diarrhea of this severity despite

		optimal symptomatic treatment and dose reduction, treatment with trial medication should be permanently discontinued.

Note: Other potential causes for diarrhea should always be considered (e.g. viral infections, bacterial overgrowth, antibiotic treatment) and treat accordingly.
*Baseline defined as usual stools/day before randomization.

Management of liver enzyme elevation:

Nintedanib can be associated with increased liver enzymes. Concomitant use of other drugs known to cause liver enzyme elevations should be evaluated. Note that liver enzymes are also muscle enzymes and may be elevated due to myositis, which leads to a concomitant increase in creatine kinase (CK). For detailed guidance on how to manage liver enzyme elevations, please refer to Table 4 below.

Table 4: Management of liver enzymes

At any study visit after Baseline visit (BL)	If AST or ALT increases to: >1.5x to <3x patient baseline levels[c].	If AST or ALT increases to: ≥3x to <5x patients baseline levels [c] and no signs of hepatic injury		If AST or ALT increases to: ≥5x to <8x patient baseline levels [c] and no signs of hepatic injury		If AST/ALT >3 with Signs of hepatic injury[a]
Action to take:	Continue trial medication as planned. Repeat AST and, ALT (LFTs), GGT, bilirubin in 2 weeks until 1.5x BL	Reduce dose or interrupt trial medication. Repeat AST and, ALT (LFTs), GGT, bilirubin in 2 weeks.		Interrupt trial medication. AST and, ALT (LFTs), GGT, bilirubin in 2 weeks.		Withdraw trial medication
Results of repeat testing after 2 weeks.		If <3x BL patient result	If ≥3x BL patient result	If <3x BL patient result	If ≥3x BL patient result	
Action to take:		If dose was reduced: returned to normal dose and monitor every 2	Permanently discontinue trial medication.	Restart at reduced dose. Monitor every 2	Permanently discontinue trial medication.	

		weeks until 1.5x BL. If interrupted: restart at a reduced dose and monitor every 2 weeks until 1.5x BL	Close observation[b]	weeks until <1.5x BL	Close observation[b]	

[a]Signs of hepatic injury are defined as

- ALT and/or AST ≥8 fold patient baseline levels
- ALT and/or AST ≥3 fold patient baseline levels and total bilirubin ≥2 fold ULN
- ALT and/or AST ≥3 fold patient baseline levels and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, and/or rash.

[b]Close observation: Re-test ALT and AST, alkaline phosphatase, total bilirubin, and GGT within 7 days, then approximately every 2 weeks until AST, ALT < 1.5 x patient baseline levels. Also, check CK along with AST and ALT to ensure elevation is not due to myositis.

[c]**Patient baseline levels (BL)** are either patient's actual baseline level of AST or ALT, OR the baseline lab's ULN of AST or ALT, whichever is higher. If the patient's baseline AST or ALT are elevated due to myositis (AST and ALT are also myositis biomarker from muscle breakdown), then patient's actual baseline levels of AST or ALT are used. However, if not, then the patient's baseline lab's ULN for AST or ALT is used. The study investigator should to repeat CK levels to determine muscle vs. liver injury.

Management of Posterior reversible encephalopathy syndrome (PRES)

Very few cases of PRES have been reported post-marketing. PRES is a neurological disorder which can present with headache, visual disturbances, seizure, lethargy, confusion, and other neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. If PRES is suspected, nintedanib treatment must be discontinued. The safety of reinitiating nintedanib therapy in patients previously experiencing PRES is not known.

6.6 Nintedanib Storage

Nintedanib should be stored in the provided pill box. No temperature monitoring is required. Nintedanib should be protected from exposure to high humidity and avoid excessive heat. Intake of all study drugs will be recorded by the patient. It will be reviewed every 4 weeks by the SS during drug accountability using visual inspection, and by reviewing the patient drug accountability form.

The medication provided for this study is for use only as directed in the protocol. A central pharmacy will be responsible for the storage, handling, and dispensing of study

drug. The Coordinating Center will monitor all documentation related to drug handling activities to ensure adherence to proper procedures.

All used and unused study drugs must be returned to the central pharmacy from patients for reconciliation and accountability and should be destroyed by the central pharmacy by authorized personnel according to approved procedures or collected by the SS or mobile home research nurse for disposal.

Study drugs are to be prescribed only by a physician named in the Form FDA-1572. Under no circumstances will the study investigator allow the study drug to be used other than as directed by the protocol.

6.7 Study Drug Labeling

The sponsor will provide the study drug and placebo. Both the study drug and placebo will contain the same labeling to ensure blinding of the subject. Study drug should be dispensed and couriered to the subject's home by the central pharmacy by the unblinded investigational pharmacist. Study medication will be labeled with the following information:

- Subject Name
- Study ID and visit numbers
- Study protocol number
- Date dispensed and expiration date
- Prescribing Study Investigator
- Administration instructions
- Investigational new drug statement
- Storage conditions

6.8 Blinding and Unblinding Procedures

This study is a double-blind trial. Trial medication is identified by a medication code number. Packaging and labeling are otherwise identical. The color, size, and shape of nintedanib and placebo capsules are indistinguishable within dose strength, but are different between dose strengths. Patients, study investigators, and everyone involved in trial conduct or analysis, or with any other interest in this double-blind trial (apart from the DSMB), will remain blinded with regard to the randomized treatment assignments until after the database lock.

The DSMB may review unblinded data upon request, and only under conditions that ensure that patients, study investigators, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded.

Emergency unblinding will be available to the study investigator, pharmacist, and investigational drug storage manager. It must only be used in an emergency situation when the identity of the trial drug must be known to the study investigator in order to provide appropriate medical treatment or otherwise assure the safety of trial subjects. The reason for unblinding must be documented in the source documents and/or appropriate case report form (CRF) page along with the date.

To avoid unblinding of the study team through drug safety reports which are to be unblinded as per regulatory requirements, a procedure will be maintained to keep code-breaking in these cases invisible to the study team.

7.0 RISK OF STUDY MEDICATION AND ADVERSE REACTIONS

7.1 Risks

- **Elevated Liver Enzymes and Drug-Induced Liver Injury:** Cases of drug-induced liver injury (DILI) have been observed with nintedanib treatment. In the clinical trials and post-marketing period, non-serious and serious cases of DILI were reported. Cases of severe liver injury with fatal outcomes have been reported in the post-marketing period. The majority of hepatic events occur within the first three months of treatment. Nintedanib was associated with elevations of liver enzymes (ALT, AST, ALKP, and GGT) and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases. Liver enzymes will be monitored in the clinical trial.

  Patients with low body weight (less than 65 kg), patients who are Asian, and female patients may have a higher risk of elevation in liver enzymes.

  In the SSc-ILD study (SENSCIS), a maximum ALT and/or AST greater than or equal to 3 times ULN was observed in 4.9% of patients treated with nintedanib.

  In the chronic fibrosing ILDs with a progressive phenotype study (INBUILD), the majority (95%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN and the majority (94%) of patients with bilirubin elevations had elevations less than 2 times ULN.

- **Gastrointestinal Disorders:** Diarrhea

  In clinical trials, diarrhea was the most frequent gastrointestinal event reported. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Modification to the study medication dosage or treatment interruptions are permitted during the trial to attempt to alleviate gastrointestinal symptoms.

In the Systemic sclerosis ILD study, diarrhea was reported in 76% of patients and led to dose reduction in 22% and discontinuation in 7% of patients.

In the chronic fibrosing ILDs with a progressive phenotype study, diarrhea was reported in 67% of patients and led to dose reduction in 16% and discontinuation in 6% of patients.

- **Gastrointestinal Disorders:** Nausea and Vomiting:

  In most patients, it is mild to moderate in severity. Modification to the study medication dosage or treatment interruptions are permitted during the trial to attempt to alleviate gastrointestinal symptoms.

  In the Systemic sclerosis ILD study, nausea and vomiting were reported in 32% and 25% of patients, respectively, and led to discontinuation in 1-2% of patients.

  In the chronic fibrosing ILDs with a progressive phenotype study, nausea and vomiting were reported in 29% and 18% of patients, respectively, and led to discontinuation in 1% of patients.

- **Arterial Thromboembolic Events:** Myocardial infarction (MI) was the most common arterial thromboembolic event, occurring in 1.5% of patients.
- **Risk of Bleeding (i.e. epistaxis):** Nintedanib may increase the risk of bleeding. In previous clinical trials, approximately 10% of patients experienced a bleeding event. Epistaxis (nose bleed) was the most frequent bleeding event. There have been post-marketing reports of non-serious and serious bleeding events, some of which were fatal.
- **Gastrointestinal Perforation:** Nintedanib may increase the risk of gastrointestinal perforation. In previous clinical trials, less than 1% of patients experienced gastrointestinal perforation. In the post-marketing period, cases of gastrointestinal perforations have been reported, some of which were fatal.
- **Nephrotic Range Proteinuria:** Cases of proteinuria (the presence of abnormal quantities of protein in the urine) have been reported in the post-marketing period.
- **Reproductive Potential:** Nintedanib may reduce fertility in females of reproductive potential.
- **Reproductive Risks / Embryo-Fetal Toxicity:** Nintedanib is a pregnancy category D medication. It can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential risk to a fetus. Women should be advised to avoid becoming pregnant while receiving nintedanib. For women of childbearing potential, the use of at least two highly effective methods of birth control is required for participation in the study. The use of highly effective contraception is required at

the initiation of treatment, during treatment, and at least 3 months after the last dose of nintedanib. The efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhea or other conditions where drug absorption may be reduced. Women taking oral hormonal contraceptives and experiencing these conditions are advised to use alternative highly effective contraception. Pregnancy status will be verified before starting nintedanib and during treatment as appropriate**.**

- **Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants from nintedanib, women will be advised that breastfeeding is not recommended during treatment.
- **Consequences of additional therapy restrictions**: There is a risk for deterioration in the subject's condition. New symptoms occurring during the treatment period requiring an unscheduled physician visit, emergency department evaluation, hospitalization, or change in immunosuppressive therapy will be evaluated by the studyinvestigator. Determination will then be made by the study investigator if additional medication is necessary.
- **Nervous System Disorders**: Posterior reversible encephalopathy syndrome (PRES) Very few cases of PRES have been reported post-marketing. PRES is a neurological disorder which can present with headache, visual disturbances, seizure, lethargy, confusion, and other neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. If PRES is suspected, nintedanib treatment must be discontinued. The safety of reinitiating nintedanib therapy in patients previously experiencing PRES is not known.

7.2 Adverse Reactions

Adverse Reactions observed in clinical trials were as follows:

Idiopathic Pulmonary Fibrosis

- The most common adverse reactions reported (greater than or equal to 5%) were diarrhea, nausea, abdominal pain, liver enzyme elevation, vomiting, decreased appetite, weight decrease, headache, and hypertension.
- The most frequent serious adverse reactions reported in patients treated with nintedanib were bronchitis (1.2%) and myocardial infarction (1.5%). The most common adverse events leading to death in nintedanib patients were pneumonia (0.7%), lung neoplasm malignant (0.3%), and myocardial infarction (0.3%).

Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype

- The most common adverse reactions included nasopharyngitis, upper respiratory infection, urinary tract infection, fatigue, and back pain.

  The most frequent serious adverse event reported was pneumonia (4%). Adverse events leading to death were reported in 3% of nintedanib patients.

  Systemic Sclerosis-Associated Interstitial Lung Disease

- The most common adverse reactions reported (greater than or equal to 5%) were diarrhea, nausea, vomiting, skin ulcer, abdominal pain, liver enzyme elevation, weight decrease, fatigue, decreased appetite, headache, pyrexia, back pain, dizziness, and hypertension.
- The most frequent serious adverse events reported were pneumonia (2.8%)

7.3 Other Potential Sides Effects of Research Procedures

- **Physical Activity Monitor (PAM) Use:** There is the possibility of minor skin irritation associated with wearing the Physical Activity Monitor wristwatch. There may be a minor risk of skin irritation from the use of the elastic belt if used with the wrist device. Keeping the band clean, dry, and loosely fitting will help reduce this risk.

- **Blood Drawing:** Subject may experience dizziness and/or fainting. The subject may experience pain, bruising, and/or bleeding at the site of the needle insertion for blood drawing. Very rarely an infection may occur at the site. The risks related to the blood draw are minimized by the procedure being done by experienced individuals and the routine use of antiseptics and pressure dressings.

- **Risk of Breach of Confidentiality:** The study data and blood specimens collected during the course of the trial will be labeled with a study code and contain no personal identifiers that could directly identify the subject. The samples and study data will be stored in a secure location; however, there is a chance that a breach of confidentiality will occur and personal or medical health information may be inappropriately distributed. Every effort will be made to ensure that this does not occur.

- Data transferred from home devices (study tablet, home spirometry, BP, and SpO2) and PAM will not contain any identifiable personal information. The data will be stored on a secure network server located in the Department of Medicine, Division of Rheumatology. Identifiable information collected by study vendors in order to perform specified study tasks will be temporarily stored on a HIPPA compliant secure network server located at each respective company location or secured cloud server.

All data related to subject's participation in the trial will be transferred to the University of Pittsburgh with identifiers removed for storage on a secure server. Study vendors will destroy all data collected during subject's participation at the conclusion of the trial.

- **Consequences of additional therapy restrictions:** Subjects will be asked to contact the study investigator regarding any deterioration in their condition. New symptoms occurring during the treatment period requiring an unscheduled physician visit, emergency department evaluation, hospitalization, or change in immunosuppressive therapy will be evaluated by the study investigator. Determination will then be made by the study investigator if additional medication is necessary.

- **Pulmonary Function Testing (PFTs):** PFTs are usually safe for most people. However, because the test may require the individual to breathe in and out quickly, he/she may feel dizzy and there is a risk that fainting may occur. The test may cause the subjects to have an asthma attack if he/she has asthma. In very rare cases, PFTs may cause a collapsed lung.

- **HRCT Chest:** Participation in this research study may involve exposure to radiation if the subjects undergo a "High Resolution" CT scan (HRCT) of the chest/lungs. The amount of radiation exposure that the subject will receive from this procedure is approximately 0.6 rem (a unit of radiation exposure) to your chest with minimal exposure of other body areas. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that a subject will receive from this study are considered to be low and comparable to everyday risks. If the subject is a woman of child-bearing potential, she may be required to have a urine pregnancy test performed before the CT scan.

- **Sit to Stand Testing:** The sit to stand test may cause temporary fatigue and shortness of breath.

8.0 SUMMARY OF ENROLLMENT AND STUDY VISITS – LOCAL SITE PATIENTS (See Schedule of Assessments – Local sites, Appendix B)

8.1 Prescreening

- Preliminary Eligibility Form completion by SS based on medical records, patient discussion, and study investigator/treating physician input.

Final review and pre-eligibility determination for screening by site study investigator (based on preliminary eligibility).

In addition, the following items will be completed only for subjects who were referred to the study, but are not active patients at the local site:

- Prescreen consent - a limited consent for prescreening procedures which includes a review of medical records and contacting the patient's myositis-ILD doctor. Prescreening consent will be obtained in person (signature in person), over the phone, or via telemedicine (with a signed form returned via Docusign, or United States Postal Service or a scanned form emailed to SS).
- Collection of contact information: name, phone, and email address
- Release of medical record form
- Treating MD approval. Approval will be documented via DocuSign

8.2 Consent Process

Fully signed consent is needed if a patient has passed prescreening and is interested in participating in the study. Consent is needed prior to conducting the screening visit and other study procedures. Consent will be obtained in person or via telemedicine (with a signed form returned via Docusign,or United States Postal Service). All video communication within the study will be conducted using a HIPAA compliant end-to-end encrypted telemedicine audio-video conference.

8.3 Service Coordination / Equipment Courier

After a patient completes the consent process, the local site will coordinate the initiation of the following services if required:

1. Mobile home research nurse (if local site plan to use them for safety and research labs).
2. Trial card. A trial card is needed if the patient will be obtaining labs, lab/clinic PFTs, or chest HRCTs from labs/centers near the patient's home.
3. PFT technician for home spirometry training and validation.

At this time point, the following study equipment will also be sent via courier to the subject by the University of Pittsburgh Coordinating Center or the appropriate medical equipment vendor. Equipment to be returned if a patient does not pass the screening or at the end of the study.

- Home spirometer
- Study tablet
- Pulse oximeter
- BP and HR monitor
- Physical Activity Monitor

8.4 Visit 0 - Screening

The visit window is up to 8 weeks. Patient can be rescreened once.

- Visit with study investigator to complete assessments (completed in person or via telemedicine)
    - Brief history
    - Brief physical
    - Review of screening form and all clinical and laboratory data

- Data Collection visit with SS. All items listed can be completed at a local site visit or done remotely through telemedicine and equipment sent to patient's home.

    - Medication review: Myositis/ILD and Concomitant medication review. For any patient that is on tacrolimus or cyclosporine, the study team will contact the prescribing physician and inform them that their patient may be randomized to a drug that can increase their blood levels of tacrolimus or cyclosporine.

    - Complete screening form including collection of demographic information
    - Home device training (study tablet, BP, HR, SpO2, physical activity monitor)
    - Review of vitals and supplemental O2 use (patient reported)
    - Sit to Stand assessment
    - Review of study drug administration

- Blood collection for labs and research serum sample. Will be completed by mobile home research nurse at home OR at a local site. Screening labs: PT/ /INR, electrolytes, AST, ALT, CK, Bilirubin, Creatinine Clearance, GGT, CBC with differential, serum pregnancy when appropriate. Note: One can perform CMP for Electrolytes, AST, ALT, Bilirubin, and Creatinine clearance.

*In the event of unforeseen issues either at the site or with mobile research nurse visits or at the site, blood collection for labs can be done at a local laboratory using the study trial card. A research serum sample will not be collected in that case.

- Height and weight (By local site or by mobile research nurse if done at patient's home). Can be substituted by the patient's self-report if required.
- In lab PFT's – collected at the local site or PFT lab near patient's home (using study trial card). If the subject has a SOC PFT completed +/- 4 weeks of screening visit, this can be used in place of conducting the research PFT. However, all subsequent PFTs are preferred to be done at the same testing location.
- Supervised Home Spirometry training and validation by PFT technician via telemedicine.
- HRCT chest per protocol if not already done as SOC within 12 weeks prior to the screening visit. Will be completed at the local site or a nearby radiology center (using study trial card).
- Final review of Inclusion/Exclusion criteria and determination of study eligibility.
- Local site coordinates with coordinating center if/when patient passed screening to arrange for services required and set up plan for subsequent visits.

Reassessment of the screening assessments is permitted one time. Please refer to the Manual of Procedures for details.

8.5 Randomization

- Local site informs central pharmacy when a patient has passed the screening requirements
- Central pharmacy
    - completes randomization form
    - dispenses the drug via specialty courier
    - communicates with patient and courier to arrange drug delivery

8.6 Visit 1 (Baseline):

Must occur within 8 weeks of the screening visit.

- Telemedicine with study investigator to complete assessments
    - Brief history
    - Brief physical
    - Review of all clinical and laboratory data

- Data Collection visit with SS will be completed remotely using HIPAA compliant end-to-end encrypted telemedicine audio-video conference.
    - Medication review: Concomitant medication review, Steroid taper and Dose modification (as needed)
    - AE monitoring
    - Flare/Rescue/End of Treatment form (as needed)
    - Visual drug inventory.
    - The subject should be instructed to perform the urine pregnancy test at the beginning of the visit if applicable. Results should be reviewed by SS within 3 minutes of test being performed.
        - *If test is positive, subject will have a serum pregnancy test done to confirm result.*
    - Review of vitals and supplemental O2 use (patient reported)
    - Device instructions and review of study tasks/procedures
    - Sit to Stand assessment
- Supervised Home Spirometry - PFT technician supervises remotely via telemedicine platform
- Patient home tasks
    - Self-administration of study medication.
    - Vital signs (BP, HR, SpO2) through monitoring device sent to patient. Site staff will transcribe the vital sign results from the MTI portal and document on vital sign form and RDMS.
    - Weight by mobile research nurse OR at local site. Can be substituted by patient's self-report if required.
    - Supplemental O2 use (patient report on the study tablet).
    - Physical Activity Monitor (PAM): Beginning the day after the baseline visit, subject will wear the physical activity monitor wrist watch for 7 consecutive days for 24 hours a day. This will be repeated every 4 weeks and start date will correspond to the push received via the tablet for PRO completion every 4 weeks). Data will automatically be transmitted from device to the portal. In instance when subject is unable to sync the PAM

device to the portal, subject will be instructed by site study coordinator to send PAM device to the site to study staff to manually download the activity data.

- Questionnaires/PROs on tablet
  - LPF
  - SGRQ
  - PROMIS- Physical Function
  - Myositis symptoms monitoring

Note: Patient assessment of change is NOT assessed at baseline.

8.7 Visit 2, 3, 5, 6 (Weeks 4, 8, 16, 20)

Study window is calculated from the date of the baseline visit +/- 5 days.

- Data collection visits with SS. Will be completed remotely using HIPAA-compliant end-to-end encrypted telemedicine audio-video conference or at local site if preferred by study investigator and subject.

  - Medication review: Concomitant medication review, Steroid taper and Dose modification (as needed)
  - AE monitoring
  - Flare/Rescue/End of Treatment form (as needed)
  - Visual drug inventory. Treatment compliance is monitored by the Sand calculated based on capsule counts: the number of capsules taken, divided by the number of capsules that should have been taken according to the scheduled period, and is then multiplied by 100.
  - The subject should be instructed to perform the urine pregnancy test at the beginning of the visit if applicable. Results should be reviewed by SS within 3 minutes of test being performed.
    - *If test is positive, subject will have a serum pregnancy test done to confirm result.*
  - Review of vitals and supplemental O2 use (patient reported)
  - Device instructions and review of study tasks/procedures

- Supervised Home Spirometry - PFT technician supervises remotely via telemedicine platform.
- Patient home tasks

- Self-administration of study medication
- Vital signs (BP, HR, SpO2) through monitoring device sent to patient. Site staff will transcribe the vital sign results from the MTI portal and document on vital sign form and RDMS.
- Weight by mobile research nurse OR at local site. Can be substituted by patient's self-report if required.
- Physical Activity Monitor (PAM): Subject will wear the physical activity wristwatch for 7 consecutive days for 24 hours a day. This will be repeated every 4 weeks from the date of the baseline visit and start date will correspond to the push received via the tablet for PRO completion. Data will automatically be transmitted from device to the portal. In instance when subject is unable to sync the PAM device to the portal, subject will be instructed by site study coordinator to send PAM device to site to manually download the activity data.
- Questionnaires/PROs on tablet
  - LPF
  - SGRQ
  - Patient assessment of change
  - PROMIS- Physical function
  - Myositis symptoms monitoring

- Courier return of left-over drug to the central pharmacy for drug accountability. Arranged by central pharmacy. Study staff should instruct subject to empty any remaining pills from study provided pill box back into the original pill bottle received from the central pharmacy.

At Visit 2 and 3 (Week 4 and 8): In addition to above:

- Blood collection for labs - full LFT's only (ALT, AST, albumin, alkaline phosphatase, direct bilirubin, total bilirubin, total protein). Will be completed at an outside lab with the use of the trial card or SOC labs can be used if done within the study visit window.

8.8 Visits 4, 7 (Weeks 12, 24)

Study window is calculated from the date of the baseline visit +/- 5 days.

- Telemedicine with study investigator to complete assessments
  - Brief history
  - Brief physical

  - Review of all clinical and laboratory data
  - Physician assessment of change form

- Data collection visit with Study Staff (SS). Will be completed remotely using HIPAA compliant end-to-end encrypted telemedicine audio-video conference or at local site if preferred by study investigator and subject.
- .
  - Medication review: Concomitant medication review, Steroid taper and Dose modification (as needed).
  - AE monitoring
  - Flare/Rescue/End of Treatment form (as needed).
  - Study drug inventory. Treatment compliance is monitored by the SS and calculated based on capsule counts: the number of capsules taken, divided by the number of capsules that should have been taken according to the scheduled period, and is then multiplied by 100.
  - The subject should be instructed to perform the urine pregnancy test at the beginning of the visit if applicable. Results should be reviewed by SS within 3 minutes of test being performed.
    - *If test is positive, subject will have a serum pregnancy test done to confirm result.*
  - Review of vitals and supplemental O2 use (patient reported)
  - Device instructions and review of study tasks/procedures
  - Sit to Stand assessment
- Blood collection for labs and research serum sample. Will be completed by mobile home research nurse at home OR at Local site. Safety monitoring labs: Electrolytes, AST, ALT, CK, Bilirubin, Creatinine Clearance, GGT, CBC with differential. Note: One can perform CMP for Electrolytes, AST, ALT, Bilirubin, and Creatinine clearance.
  * In the event of unforeseen issues either at-site or with mobile research nurse visits, blood collection for labs can be done at a local laboratory using the study trial card. A research serum sample will not be collected in that case. If the safety labs are done as SOC within the study visit window. These will be acceptable.
- Weight by mobile research nurse OR at local site. Can be substituted by patient's self-report if required.

- In lab PFT's (+/- 2 weeks) – collected local site or PFT lab near patient's home. (using study trial card). If the subject has a SOC PFT completed +/- 2 weeks of the visit, this can be used in place of conducting the research PFT. However, all subsequent PFTs are preferred to be done at the same testing location.
- Supervised Home Spirometry - PFT technician supervises remotely via telemedicine platform.
- Patient home tasks
  - Self-administration of study medication
    - Vital signs (BP, HR, SpO2) through a monitoring device sent to the patient. Site staff will transcribe the vital sign results from the MTI portal and document on vital sign form and RDMS.
  - Physical Activity Monitor (PAM): Subject will wear the physical activity wristwatch for 7 consecutive days for 24 hours a day. This will be repeated every 4 weeks from the date of the baseline visit and start date will correspond to the push received via the tablet for PRO completion. Data will automatically be transmitted from device to the portal. In instance when subject is unable to sync the PAM device subject to the portal, subject will be instructed by site study coordinator to send PAM device to site to manually download the activity data.
  - Questionnaires/PROs on tablet
    - LPF
    - SGRQ
    - Patient assessment of change
    - PROMIS- Physical Function
    - Myositis symptoms monitoring
- Courier return of left-over drug to the central pharmacy for drug accountability. Arranged by central pharmacy. Study staff should instruct subject to empty any remaining pills from the study provided pill box back into the original pill bottle received from the central pharmacy.

At Visit 7 (Week 24): In addition to the above:

- HRCT chest per protocol if not already done or planned as SOC +/- 4 weeks of the visit. Will be completed at the local site or a nearby radiology center (using a study trial card).
- Return of equipment -home spirometer, study tablet, physical activity monitor watch, Pulse oximeter, cables/USB, etc. arranged by SS

8.9 Visit 8 (Post-trial Phone Call)

28 days post Week 24 or ET visit.

- AE monitoring by SS
- Medication review by SS
- Collection of subject's perspectives about the study

8.10 Weekly Tasks

Tasks will be completed weekly by subjects and tracked by device or reported to SS. These will occur from the screening visit through the last study visit.

- Unsupervised home spirometry – to be completed twice per week by subject
- Track supplemental O2 use

8.11 Early termination (ET) / End of Treatment (EoT)

In case of early termination (ET) (i.e. discontinuation of study drug as well as study visits), an ET visit will be scheduled and completed per protocol within 10 days of stopping the clinical trial treatment prematurely. All ET/EoT visits should be documented including the date and the reasons for an unscheduled visit. In case of End of treatment (EoT, i.e. discontinuation of study drug by patient or study investigator, however continuing with study visits per protocol), an EoT visit will be scheduled and completed per protocol within 10 days of stopping clinical trial treatment prematurely. An additional AE monitoring visit will be performed 28 days (+ 5 days) after the ET or EoT visit. In the case of overlap between the EoT/ET visit or the 28 day (+ 5 days) AE monitoring visits with any of the regularly scheduled visits, SS can perform all study procedures in the same visit. See details in SUBJECT DISCONTINUATION section 10.0.

Clinical trial drug/placebo will be discontinued permanently for one or more of the following reasons for EoT:

- Patient discontinue study drug (continue study visits)
- Withdrawal of the consent (discontinue study drug and study visits)
- Out of protocol GC changes
- Out of protocol IS changes (change of agent, increase the dose, additional agent)
- Any other prohibited medication(s) or procedures
- Death

- Lung transplant
- Serious adverse event requiring stopping treatment beyond a temporary hold, including confirmed diagnosis of Posterior reversible encephalopathy syndrome
- Discontinued from the study for any reason(s); specify reason(s).

For local site patients, ET or EoT visits can be done at the site or through telemedicine as per the preference of the study investigator and patient.

- Visit with study investigator to complete assessments (completed in person or via telemedicine)
    - Brief history
    - Brief physical
    - Review of all clinical and laboratory data
    - Physician assessment of change form

- Data Collection visit with Study Staff (SS). All items listed can be completed at a local site visit or done remotely through telemedicine and monitoring devices (equipment) sent to the patient's home.
    - Medication review: Concomitant medication review, Steroid taper, and Dose modification (as needed).
    - AE monitoring
    - Flare/rescue/End of Treatment form (as needed).
    - Study drug inventory. Treatment compliance is monitored by the SS and calculated based on capsule counts. The number of capsules taken is divided by the number of capsules that should have been taken according to the scheduled period and is then multiplied by 100.
    - Review of vitals and supplemental O2 use (patient reported)
    - Sit to Stand assessment
- Blood collection for labs and research serum sample. Will be completed by a mobile home research nurse at home OR at the Local site. Safety monitoring labs: Electrolytes, AST, ALT, CK, Bilirubin, Creatinine Clearance, GGT, CBC with differential. Note: One can perform CMP for Electrolytes, AST, ALT, Bilirubin, and Creatinine clearance.
  *Note: In the event of unforeseen issues either at-site or with mobile research nurse visits, blood collection for labs can be done at a local laboratory using the study trial card. A research serum sample will not be collected in that case.

- Weight by mobile research nurse OR at Local site. Can be substituted by the patient's self-report if required.

- In lab PFT's – collected local site or PFT lab near patient's home (using study trial card) – ONLY if ET/EoT visit is >= 4 weeks from previous study PFT's or SOC PFT's completed.

- Supervised Home Spirometry - PFT technician supervises remotely a via telemedicine platform.

- HRCT chest. Study investigator to consider HRCT chest ONLY if ET/EoT visit is >= 4 weeks from previous study HCRT chest or SOC HRCT chest completed. Will be completed at the local site or a nearby radiology center (using a study trial card) within 4 weeks of ET/EoT.
- Patient home tasks
    - Vital signs (BP, HR, SpO2) through monitoring device sent to the patient. Site staff will transcribe the vital sign results from the MTI portal and document on vital sign form and RDMS.

    Physical Activity Monitor watch (Extra 7 days wearing of physical activity monitor watch to capture ET/EoT physical activity). Regularly scheduled every 4-week monitoring to continue in case of EoT. Data will automatically be transmitted from device to the portal. In instance when subject is unable to sync the PAM device to the portal, subject will be instructed by site study coordinator to send PAM device to site to manually download the activity data.

    - Questionnaires/PROs on tablet
        - LPF
        - SGRQ
        - Patient assessment of change
        - PROMIS- Physical Function
        - Myositis symptoms monitoring

- Return of equipment - home spirometer, study tablet, physical activity monitor watch, Pulse oximeter, cables/USB, etc. arranged by SS

- Courier return of left-over drug to the central pharmacy for drug accountability. Arranged by central pharmacy. Study staff should instruct subject to empty any

remaining pills from study provided pill box back into the original pill bottle received from the central pharmacy.

8.12 Unscheduled visit

Unscheduled visits can happen at the discretion of the study investigator for adverse events or flare up/worsening evaluation/monitoring. An unscheduled visit should typically occur if and when out-of-protocol treatment has been given or is planned, if and when there is a concern for a patient meeting ILD or myositis worsening criteria, or if and when the worsening criteria have been met. In addition, an unscheduled visit can be done for evaluation of adverse events (if required). If an unscheduled visit occurred due to a patient's flare up/worsening, the details should be documented, including the date and the reasons for the unscheduled visit, in the Flare/Rescue/End of Treatment form. If the unscheduled visit is related to an adverse event, the adverse event form should be updated accordingly. Unscheduled can be conducted remotely via telemedicine with a mobile research nurse, monitoring devices, and outside labs/centers or in person at the local site as per the preference of the study investigator and patient. All evaluations during an unscheduled visit are optional and to be decided at the discretion of the study investigator based on the reason for the unscheduled visit. Study investigator / SS will decide which of the following assessments are necessary at the unscheduled visit.

- Visit with study investigator to complete assessments (completed in person or via telemedicine)
    - Brief history
    - Brief physical
    - Review of all clinical and laboratory data
    - Physician assessment of change form

- Data Collection visit with Study Staff (SS). All items listed can be completed at a local site visit or done remotely through telemedicine and monitoring devices (equipment) sent to the patient's home.

    - Medication review: Concomitant medication review, Steroid taper, and Dose modification (as needed).
    - AE monitoring
    - Flare/rescue/End of Treatment form (as needed).
    - Study drug inventory. Treatment compliance is monitored by the SS and calculated based on capsule counts. The number of capsules taken is

divided by the number of capsules that should have been taken according to the scheduled period and is then multiplied by 100.

- The subject should be instructed to perform the urine pregnancy test at the beginning of the visit, if applicable. Results should be reviewed by SS within 3 minutes of test being performed.
    - *If test is positive, subject will have a serum pregnancy test done to confirm result.*
- Review of vitals and supplemental O2 use (patient reported).
- Sit to Stand assessment

- Blood collection for labs and research serum sample -collected ONLY if required by the study investigator and not done as part of SOC. Will be completed by a mobile home research nurse at home OR at the Local site. Safety monitoring labs: Electrolytes, AST, ALT, CK, Bilirubin, Creatinine Clearance, GGT, CBC with differential. Note: One can perform CMP for Electrolytes, AST, ALT, Bilirubin, and Creatinine clearance
- In the event of unforeseen issues either at-site or with mobile research nurse visits, blood collection for labs can be done at a local laboratory using the study trial card. A research serum sample will not be collected in that case.
- Weight by mobile research nurse OR at Local site. Can be substituted by the patient's self-report if required.
- In Lab PFT's – collected local site or PFT lab near patient'shome (using study trial card) – ONLY if required by the study investigator and not done as part of SOC.
- Supervised Home Spirometry -ONLY done if required by the study investigator. If needed, the PFT technician supervises remotely via a telemedicine platform.
- HRCT chest. Will be completed at the local site or a nearby radiology center (using a study trial card). ONLY if required by the study investigator and not done as part of SOC.
- Patient home tasks
    - Vital signs (BP, HR, SpO2) through monitoring device sent to the patient. Site staff will transcribe the vital sign results from the MTI portal and document on vital sign form and RDMS.
    - Questionnaires/PROs on tablet
        - LPF
        - SGRQ
        - Patient assessment of change
        - PROMIS- Physical Function

- Myositis symptoms monitoring

8.13 Post study phone call at 52 weeks

The study window is calculated from the date of the baseline visit +/- 2 weeks.

A 52 week follow up phone call will be completed to review medications as well as to record and obtain any PFT, HRCT chest done as SOC.

8.14 Compensation

Subjects will receive $100 after the baseline, the 12 week, and the 24 week visits are completed. The total compensation for the study is $300. Compensation will be provided after the visit in a format determined by each individual site.

9.0 SUMMARY OF STUDY VISITS – REMOTE PATIENTS

All remote patients will be managed remotely through the University of Pittsburgh.

9.1 Prescreening

Study advertisements will direct patients to the study's landing page. Upon review of the study information, the individual acknowledges the consent to proceed and completes the following:

- Prescreening questionnaire (via study landing page)
-
- Contact information – Registration form (via study landing page).

Site study investigator and staff:

- Obtain prescreening consent sent via DocuSign
- Obtain Release of Medical record form
- Obtain treating MD approval (Approval is to be Documented) by site study investigator
- Preliminary Eligibility Form completion by SS based on medical records, patient discussion, and study investigator/treating physician input.
- Final review and pre-eligibility determination for screening by site study investigator (based on preliminary eligibility)

9.2 Consent Process

This will occur via telemedicine where the SS and study investigator will discuss all study procedures and risk and benefits as per IRB guidelines. A tele-research web portal or similar HIPPA compliant telemedicine mobile app (such as secured Zoom or another secured telemedicine portal as per IRB guidance) will be used for consenting purposes. Remote subjects will receive a secure link to their personal email address and will be prompted to join for a one-time video conferencing session at a pre-specified date/time. The subject and study investigator will join a secure virtual conference space. Once this session is complete, the virtual room will no longer be available, and all data is encrypted throughout the session. If the patient agrees to participate after reviewing the consent form and being given the opportunity to ask any questions, the patient will sign the informed consent electronically (DocuSign) or a paper consent form as appropriate [signed consent returned via United States Postal Service (USPS) mail or scanned form emailed toS]. The signed electronic consent form is stored in the study database or if a physically signed consent form is used, it will be uploaded to the study database. Information collected from patients from the pre-screen questionnaire that do not go on to sign consent will be anonymized will all identifiers removed.

9.3 Remaining Study Visits for Remote Patients

After consent is obtained, remote study patients will follow the same assessment schedule as local site patients. , with the exception of being able to visit a local study site. All visits and assessments will take place by telemedicine with the use of home monitoring devices (equipment sent to the patient's home), through home research nurse visits, and by utilizing outside centers (for PFT, HRCT and blood collection).).

10.0 SUBJECT DISCONTINUATION

10.1 Nintedanib Stopping Rules

Trial medication must be permanently discontinued in the following circumstances:

a. Patient discontinues study treatment ("refuses treatment") or is lost to follow up.

b. Patient withdraws from the study ("refuses treatment and further visits")

c. Patient's participation is terminated by the study investigator for the event of intercurrent illness, adverse events, treatment failure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), or any reason where it is

felt by the study investigator that it is in the best interest of the patient to be terminated from the study.

d. Administration of out of protocol prohibited drugs given (i) high dose GC (> 1 mg/kg daily dose of prednisone or equivalent dose); (ii) Out of protocol and prohibited IS drugs; (iii) More than 2 IS/GC (allowable per protocol) drugs given. See clinical worsening/ flare up flow chart (Appendix A).

e. Death or lung transplant.

f. Patient experiences signs of hepatic injury or diarrhea with severity requiring permanent cessation of the trial drug as per recommendations of management of diarrhea or hepatic injury (Section 6.5, Table 2, 3, 4).

g. Pregnancy: If a patient becomes pregnant during the trial the investigational product must be stopped and the patient should be followed up until birth or otherwise termination of the pregnancy. This should be reported to IRB, DSMB, and other appropriate regulatory agencies.

Note: Patients with adverse events should first undergo dose adjustment and supportive care. Trial drug discontinuation should only be considered if the patient experiences unacceptable or refractory adverse events. Every attempt will be made to have all patients complete the remaining study visits as detailed in the Study Schedule of Assessments (Appendix B, C).

Stopping of the trial drug is highly recommended for the following situations but it remains the study investigator's decision based on a thorough assessment of all available clinical data and taking into account the risk benefits of continuing the trial drug:

a. Major surgery, including any abdominal or intestinal surgery.
b. Anti-coagulation. Patients who require full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, heparin, hirudin, direct thrombin inhibitors, etc.), or high-dose antiplatelet therapy. (Prophylactic low dose heparin or heparin flush as needed for the maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U. s.c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy is allowed.).
c. Major thrombo-embolic events e.g. stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction.
d. Increased risk of bleeding e.g. hemorrhagic CNS event, gross/frank hemoptysis or hematuria, active gastro-intestinal bleeding, or GI-ulcers.

10.2 Process for subject discontinuation

Patients have the right to withdraw from the study at any time for any reason. Every attempt will be made to have all patients complete the remaining study visits as detailed in the Study Schedule of Assessments (Appendix B)).

End of Treatment

If the patient decides to prematurely discontinue study treatment ("refuses treatment") that will not constitute withdrawal from the study. Patients should be followed for all remaining study visits as per protocol and perform all study procedures except procedures specifically related to trial drug intake. In addition, reasons for discontinuing study treatment should be documented in the Flare/Rescue/End of Treatment form. An End of Treatment (EOT) visit should be conducted at the time of discontinuation of study treatment**.** The same procedures are followed if the study investigator permanently stops the study treatment for any reason including management of the adverse event. If the patient is unable to complete all scheduled visits per protocol, obtaining information from week 12 and/or week 24 should be prioritized.

Early Termination from Study

If the patient decides to prematurely withdraw from the study ("refuses treatment and further visits"), they should be asked if they can still be contacted for further information. The outcome of that discussion should be documented by the study staff. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study in the Flare/Rescue/End of Treatment form. An Early Termination (ET) visit should be performed in such cases as well as the 28 days post trial AE monitoring follow up remote/virtual visit.

Study Investigator-Initiated Subject Withdrawal

When applicable, patients should be informed of circumstances under which their participation may be terminated by the study investigator without the patient's consent. The study investigator may withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), or any reason where it is felt by the study investigator that it is in the best interest of the patient to be terminated from the study. An Early Termination visit should be performed in such cases as well as the 28 days post trial AE monitoring follow up remote/virtual visit. The reason(s) for withdrawal must be documented and explained to the patient. If the reason for removal of a patient from the study is an adverse event, it should be documented in the study database. There should be an attempt to follow the patient until the event has resolved or stabilized.

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations before withdrawal as thoroughly as possible.

Before categorizing a patient as lost to follow-up, the study investigator must attempt to contact the patient or a responsible relative by telephone followed by registered mail to determine if any new adverse events occurred, to follow-up of any ongoing AE, and to establish as completely as possible the reason for the withdrawal.

Discontinuation of the trial by the Coordinating Center

The coordinating center reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any new safety information that could significantly affect the continuation of the trial
3. Violation of Good Clinical Practice (GCP), the Clinical Trial Protocol (CTP), or the contract disturbing the appropriate conduct of the trial.

11.0 ADVERSE EVENTS MONITORING AND REPORTING

Documented in an electronic database using standardized CTCAE v4.0 AE term definition. Adverse events are collected during the entire study period and as considered treatment-emergent from the first study drug intake until 28 days after the drug discontinuation.

11.1 Adverse Event Definition

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE:

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, physical examination, and laboratory test results, if they are judged clinically relevant by the study investigator.

All adverse events reported by the subject or observed by study site personnel from the screening visit until the completion of a subject's participation in the study (when all of the required post-dosing evaluations are completed) must be recorded in the study electronic database. Adverse events are to be recorded regardless of the relationship to the study drug.

11.2 Serious Adverse Event Definition

A serious adverse event (SAE) is defined as any AE, which fulfills at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- is deemed serious for any other reason if it is an important medical event when based on the appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or the development of dependency or abuse.

11.3 Adverse events of special interest

Adverse events relating to **gastrointestinal perforation** and **hepatic injury** will be considered as AESIs (Adverse events of special interest).

11.3.1 Definition of Hepatic Injury

Signs of hepatic injury are defined as:

- ALT and/or AST ≥8 fold patient baseline labs
- ALT and/or AST ≥3 fold patient baseline labs and total bilirubin ≥2 fold ULN
- ALT and/or AST ≥3 fold patient baseline labs and appearance of fatigue,

nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, and/or rash.

Note: ALT and/or AST may be elevated due to the myositis disease process (muscle breakdown) and are associated with CK elevation. If AST and/or ALT elevations are due to myositis, CK should be elevated and the ratio of AST or ALT by CK levels (adjusted as x ULN) should be < 2.0 and GGT should be < 2.0 x ULN.

Patient baseline levels (BL) are either patient's actual baseline level of AST or ALT, OR the baseline lab's ULN of AST or ALT, whichever is higher. If the patient's baseline AST or ALT are elevated due to myositis (AST and ALT are also myositis s biomarker from muscle breakdown), then patient's actual baseline levels of AST or ALT are used for BL. However, if not, then the patient's baseline lab's ULN for AST or ALT is used as BL. The study investigator should repeat CK levels to determine muscle vs. liver injury.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the drug-induced liver injury (DILI) checklist. Also, patients meeting the hepatic injury definition should immediately stop the trial medication. In addition, liver tests should be measured promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

Potential DILI cases are defined as AESIs and are reported and processed following the SAE process on the respective SAE form.

In the event of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) availability, the study investigator should ensure these parameters are analyzed. Should the results meet the criteria of hepatic injury, the procedures described in the DILI checklist should be followed.

11.4 AE/SAE/AESI Monitoring and Reporting

Adverse events will be documented in the electronic database using standardized CTCAE v4.0 AE term definition. The study investigator shall collect and keep detailed records of all AEs, SAEs, and AESIs from the time the informed consent is signed through the Residual Effect Period (REP). The REP is defined as 28 days after the last trial medication intake. If a subject has ended treatment, but continues with the study visits in the trial, all AEs, SAEs, and AESIs will continue to be collected. Once a subject has completed the trial, the study investigator does not need to actively monitor the patient for AEs, but should report only relevant SAEs or AESIs of which the study investigator becomes aware.

All AEs that occurred through the treatment phase and throughout the REP will be considered as on-treatment. Events that occurred after the REP will be considered as post-treatment. Adverse events are to be recorded regardless of the relationship to the study drug.

All SAEs and AESIs are required to be reported to the data coordinating center within 24 hours of the site's awareness of the event.

11.5 Intensity of Adverse Event

The intensity of the AE should be judged based on the following:

- Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated.
- Moderate: Sufficient discomfort to cause interference with usual activity.
- Severe: Incapacitating or causing an inability to work or to perform usual activities.

11.6 Causal Relationship of Adverse Event

Medical judgment should be used to determine the relationship, considering all relevant factors, including the pattern of reaction, temporal relationship, de-challenge or re-challenge, and confounding factors such as concomitant medication, concomitant diseases, and relevant history. Assessment of causal relationship should be recorded in the electronic database.

Yes (related): There is a reasonable causal relationship between the investigational product administered and the AE. Arguments that may suggest that there is a reasonable possibility of a causal relationship and the event is consistent with the known pharmacology of the drug:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative etiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).

- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if the dose is reduced).

No (not related): There is no reasonable causal relationship between the investigational product administered and the AE. Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
- Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanations (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

11.7 Responsibilities of Adverse Event Reporting to Boehringer Ingelheim (BI)

The sponsor (Coordinating center) shall report (i.e., from the time of signing the informed consent onwards through the trial until 28 days after discontinuing nintedanib) all SAEs and non-serious AEs which are relevant for a reported SAE and Adverse Events of Special Interest (AESI) by fax or other secure method using BI ECR SAE form to the BI Unique Entry Point in accordance with timeline specified in the Safety Data Exchange Agreement (Appendix to the main ECR agreement).

BI Unique Entry point (for SAE reporting):

Fax: 1-203-837-4329

E-Mail: pv_global_casemanagement@boehringer-ingelheim.com

SAE/AESI reporting timelines for Data Coordinating Center to concerned parties.

- within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event;
- within ten (10) calendar days upon receipt of any other initial and follow-up SAEs and AESIs.

For each adverse event, the study investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, causality, and action taken with the investigational drug. The study investigator will determine the expectedness of the investigational drug to the AEs as defined in the Listed Adverse Events section of the Boehringer Ingelheim's (BI's) Investigator Brochure for the Product or Product Information (PI) for the authorized Study Drug provided by BI.

The study investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the study investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol specified follow-up period), it should be reported to BI if the study investigator considers it as relevant to the BI study drug.

11.8 Pregnancy

In the rare case that a female subject or partner of a male subject participating in this clinical trial becomes pregnant after having taken trial medication, the study investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point. The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the Sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

11.9 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

11.10 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, laboratory or testing results, or any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

12.0 STATISTICAL CONSIDERATIONS

12.1 Statistical Design:

This is a multi-center double-blinded placebo-controlled study to investigate the tolerability and safety of nintedanib in combination with immunosuppressive therapy to placebo + immunosuppressive therapy in progressive myositis associated ILD. Patients will be randomized 1:1 for 12 weeks of nintedanib + SOC immunosuppressive medication vs. placebo + SOC immunosuppressive medication, followed by 12 weeks of nintedanib + SOC immunosuppressive medication for both arms.

12.2 Primary Aim and Endpoint

Change in L-PF Dyspnea score from baseline to 12 weeks.

12.3 Stratification and Randomization

Eligible patients will be randomized to either study arm in a 1:1 ratio. Randomization will be accomplished using stratified permutated blocks. The stratification factors include 1)Local vs Remote Site; 2) Mycophenolate vs. other standard of care (SOC) immunosuppressive drugs.

12.4 Patient Cohorts Used for analysis

- **Intent-to-treat cohort (ITT) -**The intent-to-treat (ITT) population (defined as all randomized patients) will be used for the analysis of the primary and secondary endpoints except toxicity. Patients will be analyzed according to their randomly assigned treatment regardless of the treatment actually received.
- **Safety cohort -** The safety population includes all patients who receive at least one dose of study therapy and will be used for the toxicity endpoint.

Patients will be analyzed according to treatment actually received, thus any patient receiving at least one dose of nintedanib/placebo will comprise the experimental group.

12.5 Full analysis set cohorts (FAS)

The 12- and 24-week full analysis set (FAS) populations will be used for the analysis of the primary, secondary, and further endpoints except toxicity. These populations are defined as:

1. 12-week full analysis set: All randomized patients with observed data in at least one endpoint through the 12-week visit;
2. 24-week full analysis set: All randomized patients with observed data in at least one endpoint through the 24-week visit.

If a patient is in the 12- or 24-week full analysis set but does not have complete follow up data on an endpoint, then analysis on that endpoint will exclude the patient or data value (as appropriate) and sensitivity analysis for the missing data will be done as appropriate. As a consequence, the actual number of patients or data points contributing to the analysis may be different from the number of subjects or planned datapoint in the selected patient set. Patients will be analyzed according to their randomly assigned treatment regardless of the treatment actually received in ITT analysis.

A per-protocol analysis cohort may be defined in a statistical analysis plan pending treatment compliance and frequency of protocol deviations.

12.6 Statistical Analysis Plan

Given the feasibility and budgetary constraints, descriptive statistics will be used for a summary of the primary and secondary endpoints between the treatments. Even though the treatment groups will be compared using statistical methods for descriptive purposes, no inferential statistics will be performed given the exploratory nature of the study. Due to a limited number of patients, no inferential comparison between treatments can be done and no causal relationship conclusion can be derived.

Continuous variables will be listed as median with interquartile and other percentages, and as mean value with standard deviation, along with minimum and maximum values (depending on the underlying distribution). Categorical values will be listed as absolute and relative frequencies. All events during follow-up will be described as incidence rates with 95% confidence intervals. Parametric or non-parametric tests will be used to compare two treatment arms (controlled and uncontrolled for covariates) for various

outcomes for descriptive purposes and to further our understanding of trends in treatment outcomes.

Further details will be included in a statistical analysis plan to assess consistency, correlation, and variation of home and clinic spirometry. Methods may include Pearson correlations and Bland-Altman plots to assess correlation; consistency will be assessed through the difference in values between home and clinic spirometry; variation will be explored within each approach.

In terms of missing data, any reasonable attempt will be undertaken to ensure the completeness of data collection. Baseline characteristics will be summarized for those patients with incomplete follow up and compared to those patients with complete follow-up. In addition, modeling approaches such as imputation may be used for patients that drop out. If differences are found, publications resulting from this analysis will include this as a limitation. Further details will be included in a more detailed statistical analysis plan.

12.7 Sample Size Calculation and Justification

This study is exploratory in nature; and the sample size is based on feasibility and budget constraints. Approximately 70 patients are expected to be randomized in the study (35 per arm) and with 20% dropout rates we expect to have 28 subjects in each arm.

In INBUILD, patients in the nintedanib and placebo arms had a mean (SD) absolute change from baseline at 12 weeks in the L-PF dyspnea score of 0.59 (13.44) and 1.45 (13.04), respectively. The minimal clinically important difference in the L-PF dyspnea score is 6.

The table below lists the width of a 2-sided 95% confidence interval for the L-PF for a variety of subgroup sizes and assumes a standard deviation of 13.44. Assuming 70 patients are enrolled and 20% of patients drop out, there will be 56 patients with complete follow up (with 28 in each arm). In each case, the confidence intervals are appropriate for an exploratory study.

Subgroup size	27	54	81	108
95% CI width	±5.07	±3.59	±2.93	±2.54

13.0 RETENTION OF RECORDS

All study records and source documents will be maintained for 7 years after the completion of the study or for the period specified by agreement with BI, whichever is longer.

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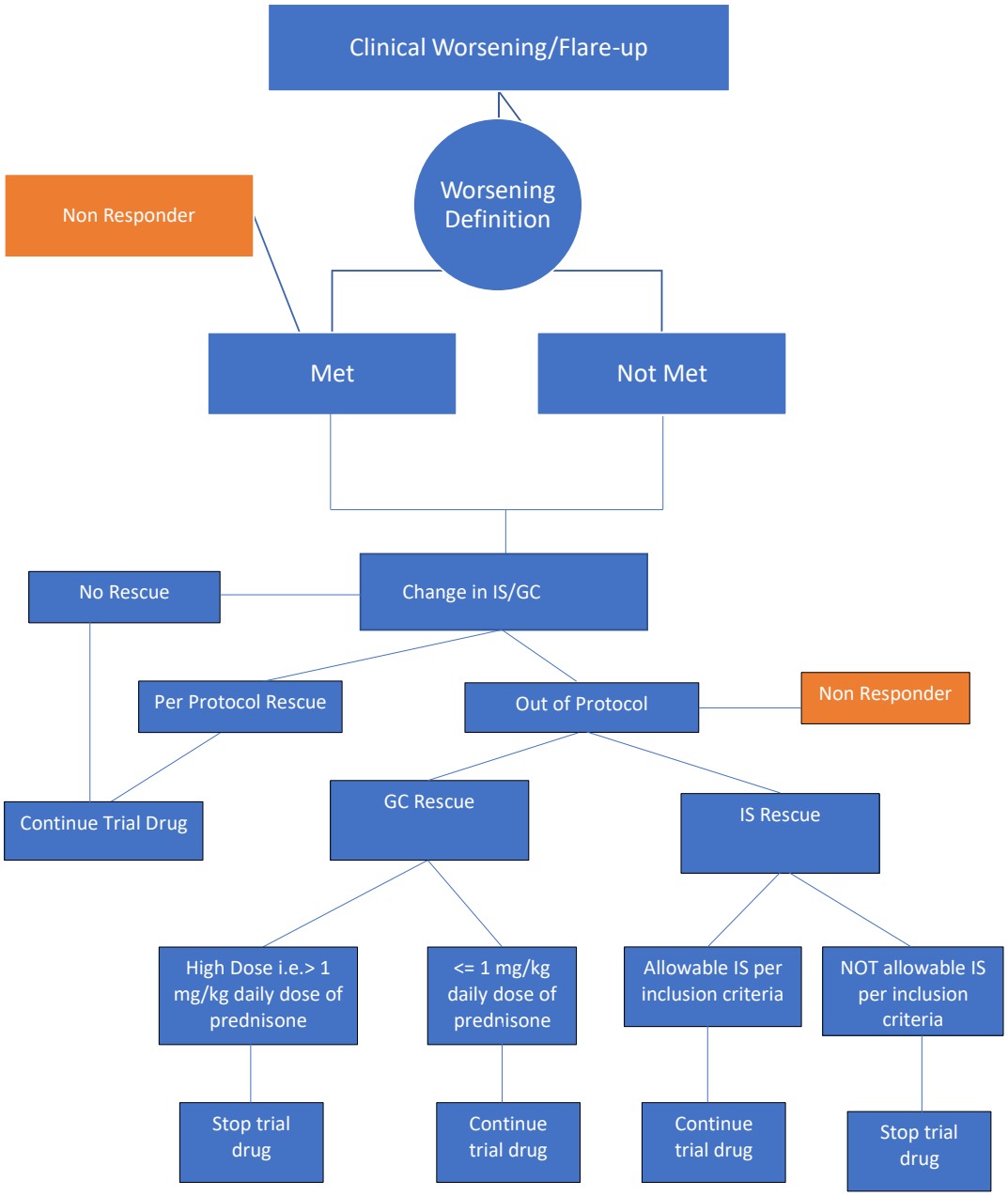
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APPENDIX A: Clinical Worsening / Flare up Flow Chart



Appendix B: Mint Trial Schedule of Assessments (SOA) – Local Patients													
Visit	**Pre-screen**	**Screen (0)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**EOT/ET**	**UNS [l]**	**9 (F/U)**
Week			**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**			**52**
Visit Window		**0-8 weeks**	**0-8 weeks**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 7 days**		**+/- 2 weeks**
Prescreen consent and medical record release (non-local site subjects only) [a]	X												
Treating MD approval [b]	X												
Informed Consent [c]		X											
Service coordination: [j]													
MTI New Patient Intake/Shipping Request Form		X											
Dispense Physical Activity monitor, pill box and urine pregnancy test (if applicable to the subject)		X											
Complete Service Request Form for outside testing		X											
Screening Criteria Form		X											
Myositis Disease and Classification Form		X											
Brief Physical Exam		X	X			X			X		X	X	
Physician assessment of change						X			X				
Initial Steroid Taper (week 4 to week 20)				X									
Demographic and Social Family History		X											
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X
Medical Comorbidities (medical history)		X											
Drug Accountability			X	X	X	X	X	X	X	X	X	X	X
Review urine pregnancy test results			X	X	X	X	X	X	X	X	X	X	X
Review of vitals (home devices) and supplemental O2 use (patient reported)			X	X	X	X	X	X	X	X	X	X	X

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Visit	**Pre-screen**	**Screen (0)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**EOT/ET**	**UNS [l]**	**9 (F/U)**
Week			**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**			**52**
Visit Window		**0-8 weeks**	**0-8 weeks**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 7 days**		**+/- 2 weeks**
Training and proficiency testing of Home spirometry by MTI PFT technician through telemedicine		X											
Blood collection for research repository													
Screening & Safety labs [d,e]													
• PT/INR/Serum pregnancy WOCBP- **Screening only**													
• AST, ALT													
• Electrolytes		X				X			X		X	X	
• CK													
• Bilirubin													
• Creatinine Clearance													
• GGT													
• CBC with differential													
Blood Collection for full LFT's [e]				X	X								
Weight measurement [f]		X				X			X		X		
Height measurement [f]		X											
Eligibility Review Request for Randomization		X											
Infuserve Drug Order Form			X			X [k]							
Review urine pregnancy testing for women of WOCBP			X	X	X	X	X	X	X		X		
In Lab/clinic PFT's: By local site or PFT lab near patients home[j] (+/- 2 weeks) [g]		X				X			X		X	X	

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Visit	**Pre-screen**	**Screen (0)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**EOT/ET**	**UNS [l]**	**9 (F/U)**
Week			**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**			**52**
Visit Window		**0-8 weeks**	**0-8 weeks**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 7 days**		**+/- 2 weeks**
HRCT Chest: By local site or radiology center near patient's home [h, i]		X							X		X	X	
Supervised Home Spirometry: By MTI PFT technician via telemedicine.			X	X	X	X	X	X	X		X	X	
Sit to Stand- By telemedicine		X	X			X			X		X	X	
Vital Signs. Performed weekly by patient.		X	X	X	X	X	X	X	X		X	X	
• BP, HR, SpO2 – via home devices													
• Supplemental O2 use (patient report on the study tablet).													
Unsupervised Home Spirometry. Performed twice per week by patient.			X	X	X	X	X	X	X				
Patient Questionnaires/PROs: by patient via home tablet			X	X	X	X	X	X	X		X	X	
• L-PF			X	X	X	X	X	X	X		X	X	
• SGRQ			X	X	X	X	X	X	X		X	X	
• PROMIS-physical function short form			X	X	X	X	X	X	X		X	X	
• Myositis Symptoms Monitoring			X	X	X	X	X	X	X		X	X	
• Patient overall assessment of change				X	X	X	X	X	X		X	X	
Physical Activity monitor: SS instructs usage at baseline & prn [m]			X	X	X	X	X	X	X		X		
Patient wears 7 consecutive days every 4 weeks after each study visit [m]			X	X	X	X	X	X	X		X		

Appendix B: Mint Trial Schedule of Assessments (SOA) – Local Patients													
Visit	**Pre-screen**	**Screen (0)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**EOT/ET**	**UNS** [i]	**9 (F/U)**
Week			**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**			**52**
Visit Window		**0-8 weeks**	**0-8 weeks**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 7 days**		**+/- 2 weeks**
Subject return of unused IMP and bottles to Central Pharmacy				X	X	X	X	X	X		X		
Patient's perspective about the trial (patient questionnaire)										X			
Randomization by Central Pharmacy			X										
Daily self-administration of study medication			X	X	X	X	X	X					
Review medications and any SOC PFT or HCRT results													X
Flare/Rescue form			Required if myositis or ILD worsening criteria met										
AE monitoring				X	X	X	X	X	X	X	X	X	X

It is highly encouraged all visits subsequent study visits after screening visit be performed virtually, but if preferred by study investigator can be performed on site.
a. Prescreen activities (in person, via phone or telemedicine with the review of medical records
b. Only for subjects that are not active patients at the local site
c. Full consent through telemedicine or at site
d. Completed by PCM nurse, in person at local site or outside testing center near patient home.
e. Outside testing lab using sponsor provided payment card (SOC labs can be used if done within the study visit window) - AST, ALT, albumin, alkaline phosphatase, direct bilirubin, total bilirubin, total protein
f. Can be completed in person at local site, by home nurse or self reported by subject.
g. As per protocol at screening (if not done as per SOC within in 3 months prior to the screening visit)
h. As per protocol (*at 24 weeks (+/- 4 weeks) of the visit) if not already done or planned as SOC within +/- 4 weeks.
i. If ET/EoT then study investigator to consider HRCT chest within 4 weeks of ET/EoT visit (if >= 4 week since last HRCT chest)

j. To be returned at visit 7 or ET visit
k. Open label drug order form
l. Determination of assessments is at the discretion of the site investigator m. SC needs to ensure Physical Activity Monitor (PAM) is worn by subject for a minimum of 4 days out of 7 consecutive days and each day should be at least 12 hours a day of wear time.